HEPATITIS C VIRUS INHIBITORS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/156,131 filed February 27, 2009 and U.S. Provisional Application No. 61/158,071 filed March 6, 2009. The entire teachings of the above applications are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to novel antiviral agents. More specifically, the present invention relates to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, methods for inhibiting HCV viral replication, methods for treating or preventing HCV infection, and processes for making the compounds.

BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K. L. (1997) Hepatology 26 (suppl 1): 71S-77S). This therapy remains less effective

against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of responders, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non-A, non-B hepatitis (NANBH) (Kuo, G et al (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae*, such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) Science 244:359-362; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al 'An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' RNA – A Publication of the RNA Society. l(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded

proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) Virology 2nd Edition, p931-960; Raven Press, N.Y.). There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are several non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease. NS5A is a membrane-anchored phosphoprotein that is observed in basally phosphorylated (56 kDa) and hyperphosphorylated (58 kDa) forms. While its function has not fully been elucidated, NS5A is believed to be important in viral replication. The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. *et al* (1996) *EMBO J.* 151 2-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype la and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.* (2000) *Journal of Virology*, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to be useful to treat HCV infection.

Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. *et al* (1996) J. Virology 70:3363-3371; Tanaka, T. *et al* (1995) Biochem Biophys. Res. Commun. 215744-749; Tanaka, T. *et al* (1996) J. Virology 70:3307-3312; Yamada, N. *et al* (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A

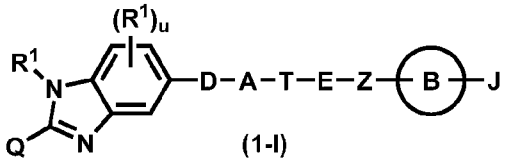
protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, 284, 1; and in Rice, C. M. *Nature* 2005, 435, 374.

Based on the foregoing, there exists a significant need to identify compounds with the ability to inhibit HCV. A general strategy for the development of antiviral agents is to inactivate virally encoded proteins, including NS5A, that are essential for the replication of the virus. The relevant patent disclosures describing the synthesis of HCV NS5A inhibitors are: US 2009/0202478; US 2009/0202483; WO 2009/020828; WO 2009/020825; WO 2009/102318; WO 2009/102325; WO 2009/102694; WO 2008/144380; WO 2008/021927; WO 2008/021928; WO 2008/021936; WO 2006/133326; WO 2004/014852; WO 2008/070447; WO 2009/034390; WO 2006/079833; WO 2007/031791; WO 2007/070556; WO 2007/070600; WO 2008/064218; WO 2008/154601; WO 2007/082554; and WO 2008/048589; the contents of each of which are expressly incorporated by reference herein.

SUMMARY OF THE INVENTION

The present invention relates to novel antiviral compounds represented herein below, pharmaceutical compositions comprising such compounds, and methods for the treatment or prophylaxis of viral (particularly HCV) infection in a subject in need of such therapy with said compounds. Compounds of the present invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents.

In its first principal aspect, the present invention provides a compound of Formula (**1-I**)



(1-I)

or a pharmaceutically acceptable salt thereof, wherein:

D and Z are are each independently absent or optionally substituted linear aliphatic group containing zero to eight carbon atoms;

A and E are are each independently absent or a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkenyl, each optionally substituted;

T is absent or an optionally substituted aliphatic group;

Wherein one to four of A, D, E, T and Z is absent;

Ring B is a five-membered heteroaryl wherein said heteroaryl is optionally substituted; preferably, a five-membered heteroaryl containing one or more nitrogen atoms; more preferably, imidazolyl that is C-attached to group J and one of groups Z, E, T, A and D;

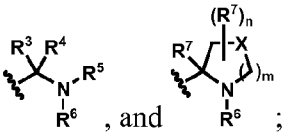
R^1 at each occurrence is independently selected from the group consisting of hydrogen, halogen, cyano, optionally substituted C_1-C_4 alkyl, $-O-R^{11}$, $-NR^aR^b$, $-C(O)R^{11}$, $-CO_2R^{11}$, and $-C(O)NR^aR^b$; preferably, hydrogen, halogen and optionally substituted C_1-C_4 alkyl;

R^{11} at each occurrence is independently hydrogen or optionally substituted C_1-C_8 alkyl; and

R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_8 alkyl, and optionally substituted C_2-C_8 alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

u at each occurrence is independently 1, 2, or 3;

Q and J are each independently selected from:



, and ;

R^3 and R^4 at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_3-C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1-C_4 alkyl; or alternatively, R^3 and R^4 can be taken together with the carbon atom to which they are attached to form optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic;

R^5 at each occurrence is independently hydrogen, optionally substituted C_1-C_8 alkyl, or optionally substituted C_3-C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1-C_4 alkyl;

R^6 at each occurrence is independently selected from the group consisting of $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$, preferably $-C(O)-R^{12}$, more preferably an optionally substituted amino acid acyl;

R^{12} at each occurrence is independently selected from the group consisting of $-O-R^{11}$, $-NR^aR^b$, $-R^{13}$, and $-NR^cR^d$, preferably optionally substituted C_1-C_8 alkyl and $-O-R^{11}$;

R^{13} at each occurrence is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; preferably optionally substituted C_1-C_8 alkyl; more preferably C_1-C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or $O(C_1$-C_4 alkyl); and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, $-R^{13}$, $-C(O)-R^{13}$, $-C(O)-OR^{13}$, $-S(O)_2-R^{13}$, $-C(O)N(R^{13})_2$, and $-S(O)_2N(R^{13})_2$;

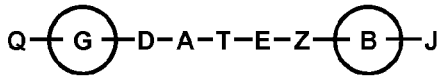
m is 0, 1, or 2, preferably 1;

n is 1, 2, 3, or 4, preferably 1 or 2;

X at each occurrence is independently selected from O, S, S(O), SO_2, and $C(R^7)_2$, preferably CH_2 or CHR^7; provided that when m is 0, X is $C(R^7)_2$; and

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, cyano, $-O-R^{11}$, $-NR^aR^b$, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted $-C_1$-C_4 alkyl; preferably, hydrogen, methyl or halogen; or two vicinal R^7 groups are taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring; preferably, a fused, optionally substituted cyclopropyl; or alternatively two geminal R^7 groups are taken together with the carbon atom to which they are attached to form a spiro, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl.

In its second principal aspect, the present invention provides a compound of Formula (**2-I**)



(2-I)

or a pharmaceutically acceptable salt thereof, wherein:

D and Z are are each independently absent or optionally substituted linear aliphatic group containing zero to eight carbon atoms;

A and E are are each independently absent or a cyclic group independently selected from aryl, heteroaryl, heterocyclic, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkenyl, each optionally substituted;

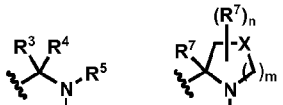
T is absent or an optionally substituted aliphatic group;

Wherein one to four of A, D, E, T and Z is absent;

Ring B is a five-membered heteroaryl or a 5/6-membered fused heteroaryl, wherein the 6-membered ring of said 5/6-membered fused heteroaryl is attached to one of groups Z, E, T, A and D, and the 5-membered ring of said 5/6 membered fused heteroaryl is attached to group J and contains one or more nitrogen atoms; wherein said five-membered heteroaryl or 5/6-membered fused heteroaryl is optionally substituted; preferably imidazolyl or benzimidazolyl, wherein said imidazolyl or benzimidazolyl are C-attached to group J and one of groups Z, E, T, A and D;

Ring G is a 5/6-membered fused heteroaryl other than benzimidazolyl, wherein the 6-membered ring of said 5/6-membered fused heteroaryl is attached to one of groups D, A, T, E and Z, and the 5-membered ring of said 5/6-membered fused heteroaryl is attached to group Q and contains one or more nitrogen atoms; and wherein said 5/6-membered fused heteroaryl is optionally substituted;

Q and J are each independently selected from:



, and ;

R^3 and R^4 at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, and optionally substituted C_3-C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1-C_4 alkyl; or alternatively, R^3 and R^4 can be taken together with the carbon atom to which they are attached to form optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic;

R^5 at each occurrence is independently hydrogen, optionally substituted C_1-C_8 alkyl, or optionally substituted C_3-C_8 cycloalkyl; preferably hydrogen or optionally substituted C_1-C_4 alkyl;

R^6 at each occurrence is independently selected from the group consisting of $-C(O)-R^{12}$, $-C(O)-C(O)-R^{12}$, $-S(O)_2-R^{12}$, and $-C(S)-R^{12}$, preferably $-C(O)-R^{12}$, more preferably an optionally substituted amino acid acyl;

R^{12} at each occurrence is independently selected from the group consisting of $-O-R^{11}$, $-NR^aR^b$, $-R^{13}$, and $-NR^cR^d$, preferably optionally substituted C_1-C_8 alkyl and $-O-R^{11}$;

R^{11} at each occurrence is independently hydrogen or optionally substituted C_1-C_8 alkyl; and

R^a and R^b at each occurrence are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_8 alkyl, and optionally substituted C_2-C_8 alkenyl; or R^a and R^b can be taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or optionally substituted heteroaryl group;

R^{13} at each occurrence is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, heterocyclic, aryl, and heteroaryl, each optionally substituted; preferably optionally substituted C_1-C_8 alkyl; more preferably C_1-C_8 alkyl optionally substituted with amino, hydroxy, optionally substituted phenyl, protected amino, or $O(C_1$-C_4 alkyl); and

R^c and R^d at each occurrence are each independently selected from the group consisting of hydrogen, $-R^{13}$, $-C(O)-R^{13}$, $-C(O)-OR^{13}$, $-S(O)_2-R^{13}$, $-C(O)N(R^{13})_2$, and $-S(O)_2N(R^{13})_2$;

m is 0, 1, or 2, preferably 1;

n is 1, 2, 3, or 4, preferably 1 or 2;

X at each occurrence is independently selected from O, S, S(O), SO_2, and $C(R^7)_2$, preferably CH_2 or CHR^7; provided that when m is 0, X is $C(R^7)_2$; and

R^7 at each occurrence is independently selected from the group consisting of hydrogen, halogen, cyano, $-O-R^{11}$, $-NR^aR^b$, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted $-C_1$-C_4 alkyl; preferably hydrogen, methyl or halogen; or two vicinal R^7 groups are taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring; preferably a fused, optionally substituted cyclopropyl; or alternatively two geminal R^7 groups are taken together with the carbon atom to which they are attached to form a spiro, optionally substituted C_3-C_8 cycloalkyl or optionally substituted heterocyclic ring; preferably a spiro, optionally substituted cyclopropyl.

Each preferred group stated above can be taken in combination with one, any or all other preferred groups.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In yet another aspect, the present invention provides a method of inhibiting the replication of a RNA-containing virus comprising contacting said virus with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. Particularly, this invention is directed to methods of inhibiting the replication of HCV.

In still another aspect, the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. Particularly, this invention is directed to methods of treating or preventing infection caused by HCV.

Yet another aspect of the present invention provides the use of a compound or combination of compounds of the present invention, or a therapeutically acceptable salt thereof, as defined hereinafter, in the preparation of a medicament for the treatment or prevention of infection caused by RNA-containing virus, specifically HCV.

DETAILED DESCRIPTION OF THE INVENTION

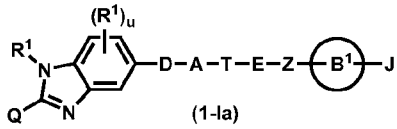
The compounds of the invention have utility in inhibiting the replication of RNA-containing virus, including, for example, HCV. Other compounds useful for inhibiting the replication of RNA-containing viruses and/or for the treatment or prophylaxis of HCV infection have been described in copending U.S. Application Serial No. 12/702,673 filed February 9, 2010 entitled "Linked Dibenzimidazole Antivirals"; U.S. Application Serial No. 12/702,692 filed February 9, 2010 entitled "Linked Dibenzimidazole Derivatives"; U.S. Application Serial No. 12/702,802 filed February 9, 2010 entitled "Linked Dibenzimidazole Derivatives"; U.S. Application Serial No. 12/707,190 filed February 17, 2010 entitled "Linked

Diimidazole Antivirals"; U.S. Application Serial No. 12/707,200 filed February 17, 2010 entitled "Linked Diimidazole Derivatives"; and U.S. Application Serial No. 12/707,210 filed February 17, 2010 entitled "Hepatitis C Virus Inhibitors"; the contents of each of which are expressly incorporated by reference herein.

I. Compounds having Formula (**1-I**)

In certain aspects, the present invention relates to compounds of Formula (**1-I**) as illustrated above, or a pharmaceutically acceptable salt thereof.

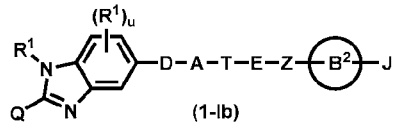
In one embodiment, the present invention relates to compounds of Formula (**1-Ia**), or a pharmaceutically acceptable salt thereof:



(1-Ia)

wherein A, D, E, T, Z, Q, J, u, and R^1 are as previously defined in Formula (**1-I**) and Ring B^1 is a five-membered heteroaryl that is C-attached to J and to one of Z, E, T, A and D.

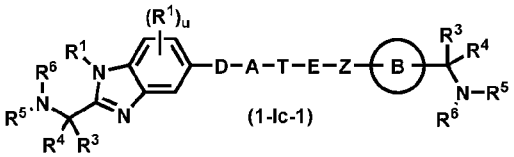
In another embodiment, the present invention relates to compounds of Formula (**1-Ib**), or a pharmaceutically acceptable salt thereof:



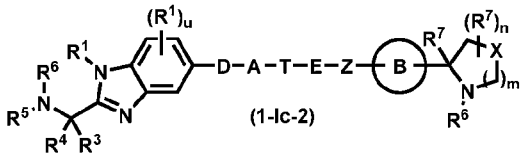
(1-Ib)

wherein A, D, E, T, Z, Q, J, u, and R^1 are as previously defined in Formula (**1-I**) and Ring B^2 is selected from imidazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiazolyl, and isoxazolyl; and Ring B^2 is C-attached to J and to one of Z, E, T, A and D.

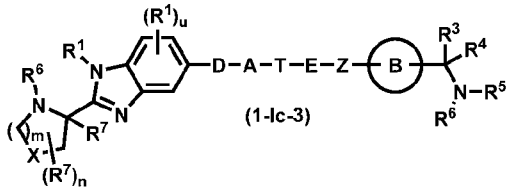
In yet another embodiment, the present invention relates to compounds of Formulae (**1-Ic-1** to **1-Ic-4**), or a pharmaceutically acceptable salt thereof:



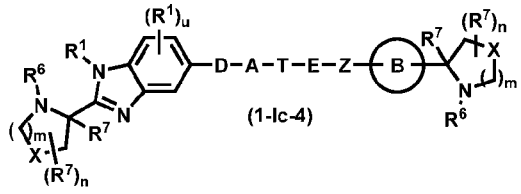
(1-Ic-1)



(1-Ic-2)



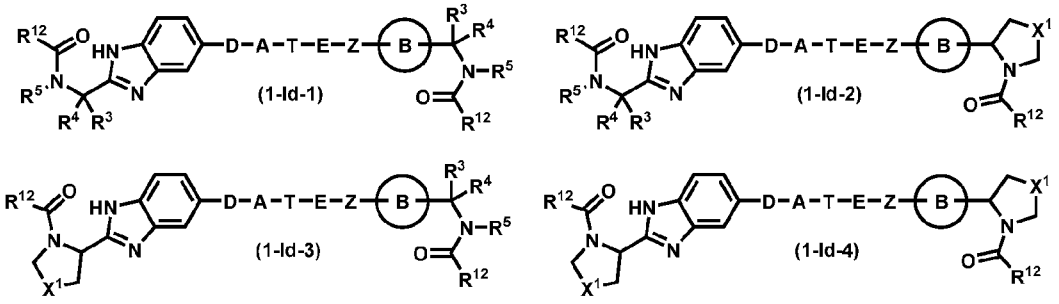
(1-Ic-3)



(1-Ic-4)

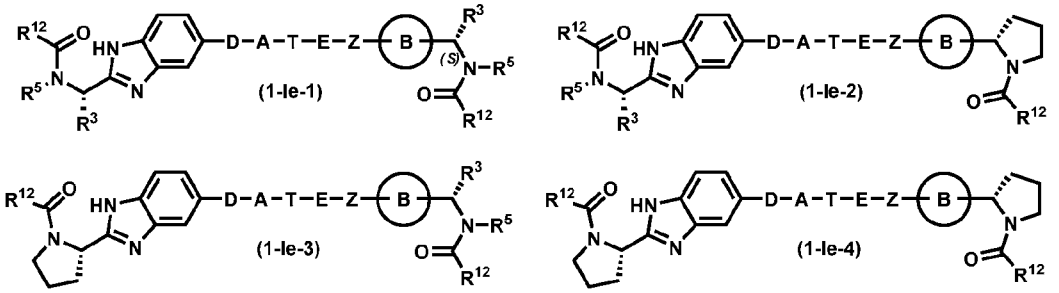
wherein A, D, E, T, Z, Ring B, X, u, m, n, R^1, R^3, R^4, R^5, R^6 and R^7 are as previously defined in Formula (**1-I**).

In still another embodiment, the present invention relates to compounds of Formulae (**1-Id-1** to **1-Id-4**), or a pharmaceutically acceptable salt thereof:



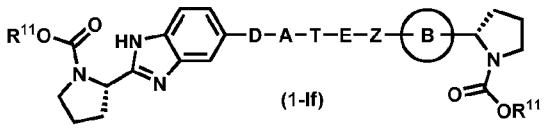
wherein A, D, E, T, Z, Ring B, R^3, R^4, R^5, and R^{12} are as previously defined in Formula (**1-I**) and X^1 is independently CH_2, CHF, CH(OH), or CF_2.

In still another embodiment of the present invention, the absolute stereochemistry of the pyrrolidine and 2-benzimidazolylmethylamine or five-membered heteroarylmethylamine moiety is represented by Formulae (**1-Ie-1** to **1-Ie-4**):



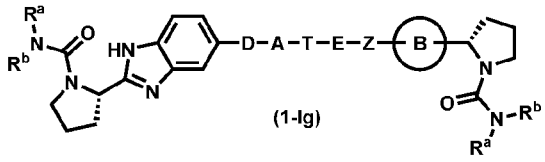
wherein A, D, E, T, Z, Ring B, R^3, R^5, and R^{12} are as previously defined in Formula (**1-I**).

In still another embodiment, the present invention relates to compounds of Formula (**1-If**), or a pharmaceutically acceptable salt thereof:



wherein A, D, E, T, Z, Ring B, and R^{11} are as previously defined in Formula (**1-I**).

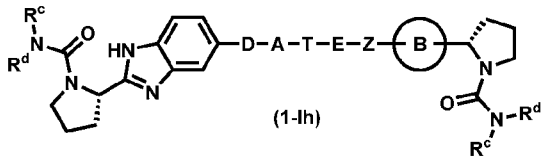
In still another embodiment, the present invention relates to compounds of Formula (**1-Ig**), or a pharmaceutically acceptable salt thereof:



(1-Ig)

wherein A, D, E, T, Z, Ring B, R^a and R^b are as previously defined in Formula (**1-I**).

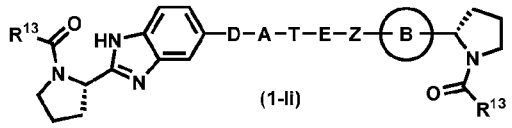
In still another embodiment, the present invention relates to compounds of Formula (**1-Ih**), or a pharmaceutically acceptable salt thereof:



(1-Ih)

wherein A, D, E, T, Z, Ring B, R^c and R^d are as previously defined in Formula (**1-I**).

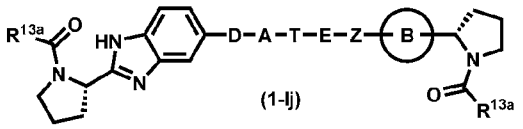
In still another embodiment, the present invention relates to compounds of Formula (**1-Ii**), or a pharmaceutically acceptable salt thereof:



(1-Ii)

wherein A, D, E, T, Z, Ring B, and R^{13} are as previously defined in Formula (**1-I**).

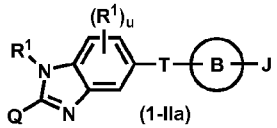
In still another embodiment, the present invention relates to compounds of Formula (**1-Ij**), or a pharmaceutically acceptable salt thereof:



(1-Ij)

wherein A, D, E, T, Z, Ring B are as previously defined in Formula (**1-I**) and R^{13a} at each occurrence is independently an optionally substituted C_1-C_8 alkyl; preferably C_1-C_8 alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C_1-C_4 alkyl).

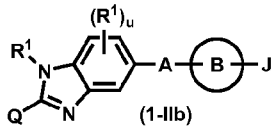
In still another embodiment, the present invention relates to compounds of Formula (**1-IIa**), or a pharmaceutically acceptable salt thereof:



(1-IIa)

wherein Q, J, Ring B, u, and R^1 are as previously defined in Formula (**1-I**) and T is present and as previously defined in Formula (**1-I**).

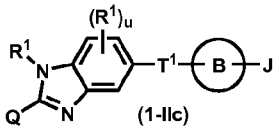
In still another embodiment, the present invention relates to compounds of Formula (**1-IIb**), or a pharmaceutically acceptable salt thereof:



(1-IIb)

wherein Q, J, Ring B, u, and R^1 are as previously defined in Formula (**1-I**) and A is present and as previously defined in Formula (**1-I**).

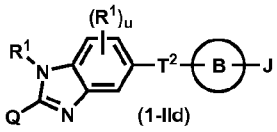
In still another embodiment, the present invention relates to compounds of Formula (**1-IIc**), or a pharmaceutically acceptable salt thereof:



(1-IIc)

wherein Q, J, Ring B, u, and R^1 are as previously defined in Formula (**1-I**) and T^1 is a linear aliphatic group, optionally containing one or more of an olefinic double bond and an alkynic triple bond and further, optionally comprising one or more groups selected from the group consisting of O, $N(R^{11})$, C(O), $S(O)_2$, C(O)O, $C(O)N(R^{11})$, OC(O)O, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$.

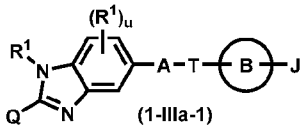
In still another embodiment, the present invention relates to compounds of Formula (**1-IId**), or a pharmaceutically acceptable salt thereof:



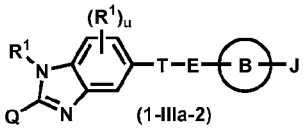
(1-IId)

wherein Q, J, Ring B, u, and R^1 are as previously defined in Formula (**1-I**) and T^2 is an aliphatic group comprising a C_3-C_8 cycloalkyl or C_3-C_8 cycloalkenyl and optionally contains one or more of an olefinic double bond and an alkynic triple bond and further, optionally comprises one or more groups selected from the group consisting of O, $N(R^{11})$, C(O), $S(O)_2$, C(O)O, $C(O)N(R^{11})$, OC(O)O, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$.

In still another embodiment, the present invention relates to compounds of Formulae (**1-IIIa-1** and **1-IIIa-2**), or a pharmaceutically acceptable salt thereof:



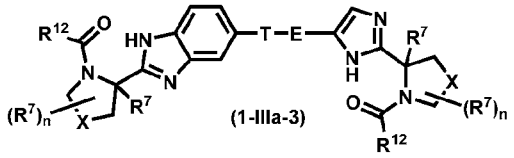
(1-IIIa-1)



(1-IIIa-2)

wherein Q, J, Ring B, u, and R^1 are as previously defined in Formula (**1-I**); in Formula (**1-IIIa-1**) A and T are each present and as previously defined in Formula (**1-I**); and in Formula (**1-IIIa-2**), T and E are each present and as previously defined in Formula (**1-I**).

In still another embodiment, the present invention relates to compounds of Formula (**1-IIIa-3**), or a pharmaceutically acceptable salt thereof:

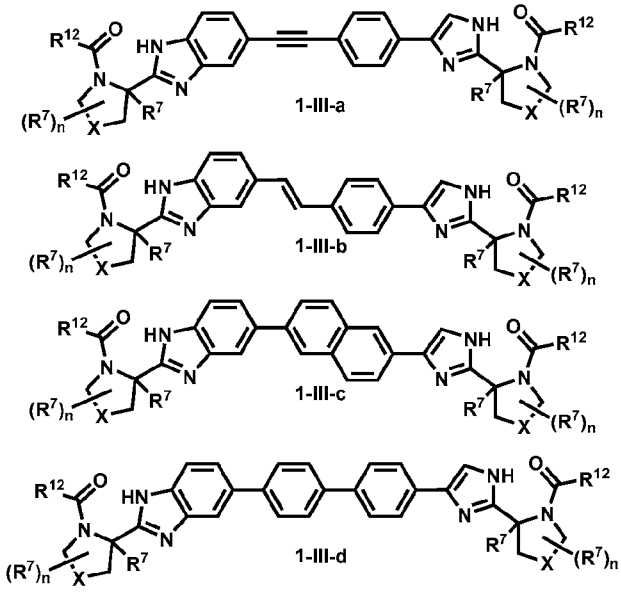


wherein n is 1 or 2; T is absent or optionally substituted C_2-C_4 alkenyl or optionally substituted C_2-C_4 alkynyl; E is phenyl, monocyclic heteroaryl, bicyclic aryl, or bicyclic heteroaryl, each optionally substituted; X at each occurrence is independently CH_2, CHF, CH(OH), CHMe, CF_2, or $C(R^7)_2$; wherein R^7 at each occurrence is independently hydrogen or methyl; alternatively, the two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro, optionally substituted C_3-C_8 cycloalkyl; or yet alternatively, two vicinal R^7 groups are taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C_3-C_8 cycloalkyl; and R^{12} at each occurrence is independently optionally substituted C_1-C_8 alkyl. In certain aspects, the invention is a compound of Formula (**1-IIIa-3**) wherein R^{12} at each occurrence is independently C_1-C_8 alkyl substituted with -$NHCO_2$(C_1-C_4 alkyl) or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formula (**1-IIIa-3**), or a pharmaceutically acceptable salt thereof; wherein two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formula (**1-IIIa-3**), or a pharmaceutically acceptable salt thereof; wherein two vicinal R^7 groups are taken together with the two adjacent atoms to which they are attached to form a fused cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or O(C_1-C_4 alkyl).

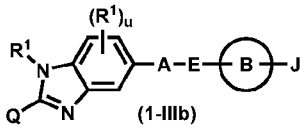
In still another embodiment, the present invention relates to compounds of Formulae (**1-III-a**) to (**1-III-d**), or a pharmaceutically acceptable salt thereof:



wherein n is 1 or 2; X at each occurrence is each independently CH_2, CHF, CH(OH), CHMe, CF_2, or $C(R^7)_2$; wherein R^7 at each occurrence is independently hydrogen or methyl; alternatively, the two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro cyclopropyl; or yet alternatively, two vicinal R^7 groups are taken together with the two adjacent atoms to which they are attached to form a fused cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1$-C_4 alkyl).

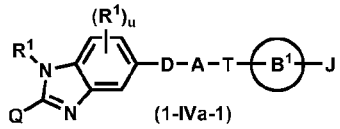
In still another embodiment, the present invention relates to compounds of Formulae (**1-III-a**) to (**1-III-d**); wherein R^{12} at each occurrence is independently C_1-C_8 alkyl substituted with $-NHCO_2(C_1$-C_4 alkyl) or $O(C_1$-C_4 alkyl); or a pharmaceutically acceptable salt thereof.

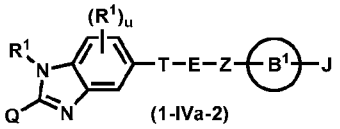
In still another embodiment, the present invention relates to compounds of Formula (**1-IIIb**), or a pharmaceutically acceptable salt thereof:



wherein Q, J, Ring B, u, and R^1 are as previously defined; A and E are each present and as previously defined in Formula (**1-I**).

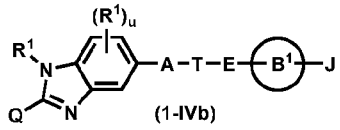
In still another embodiment, the present invention relates to compounds of Formulae (**1-IVa-1** and **1-IVa-2**), or a pharmaceutically acceptable salt thereof:





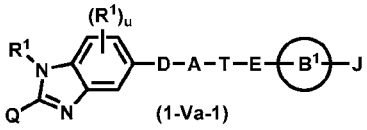
wherein Ring B^1, Q, J, u, and R^1 are as previously defined in Formula (**1-I**); in Formula (**1-IVa-1**), A, D, and T are each present and as previously defined in Formula (**1-I**); and in Formula (**1-IVa-2**), E, T, and Z are each present and as previously defined in Formula (**1-I**).

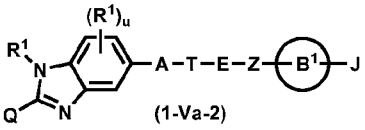
In still another embodiment, the present invention relates to compounds of Formula (**1-IVb**), or a pharmaceutically acceptable salt thereof:



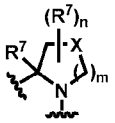
wherein Ring B^1, Q, J, u, and R^1 are as previously defined in Formula (**1-I**); A, E, and T are each present and as previously defined in Formula (**1-I**).

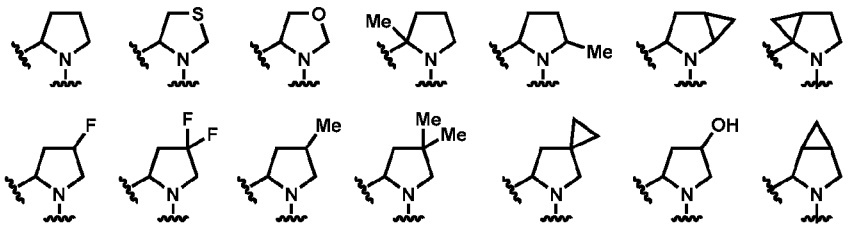
In still another embodiment, the present invention relates to compounds of Formulae (**1-Va-1** and **1-Va-2**), or a pharmaceutically acceptable salt thereof:



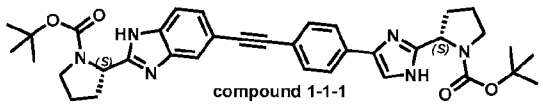


wherein Ring B^1, Q, J, u, and R^1 are as previously defined in Formula (**1-I**); in Formula (**1-Va-1**), D, A, T and E are each present and as previously defined in Formula (**1-I**); in Formula (**1-Va-2**), A, E, T, and Z are each present and as previously defined in Formula (**1-I**).

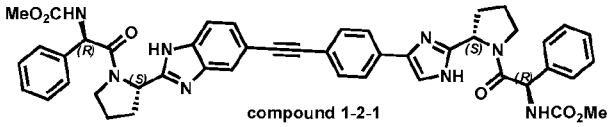
In still another embodiment, the present invention relates to compounds of Formula (**1-I**), or a pharmaceutically acceptable salt thereof; wherein  at each occurrence is independently illustrated by one of the following groups:



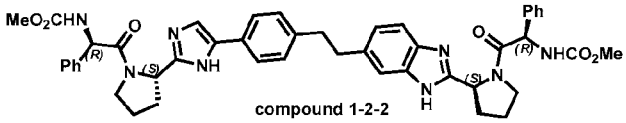
Representative compounds of the present invention are those selected from compounds 1-1-1, 1-2-1, and 1-2-2 (shown below), and compounds 1-1 to 1-545 compiled in Tables 1-9:



compound 1-1-1



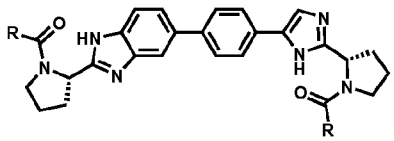
compound 1-2-1

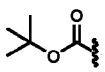
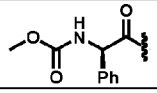
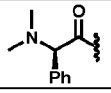
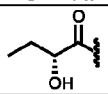
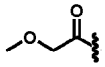
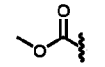
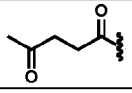
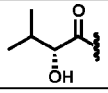
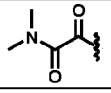
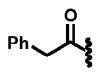
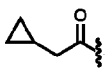
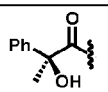
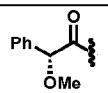
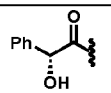
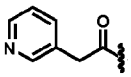
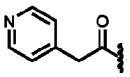
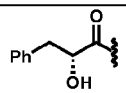
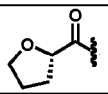
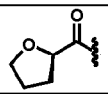
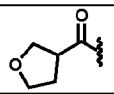


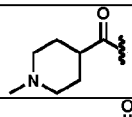
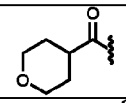
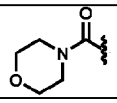
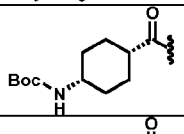
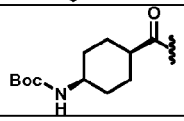
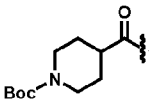
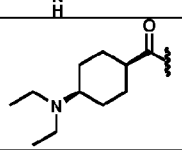
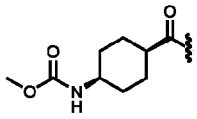
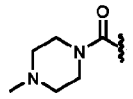
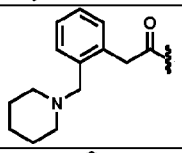
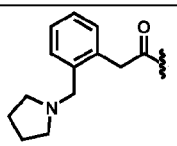
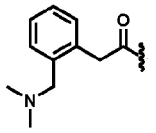
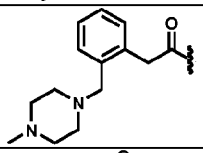
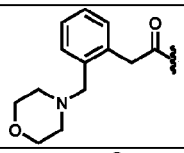
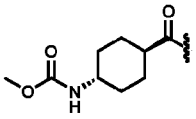
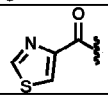
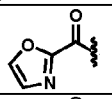
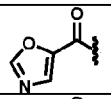
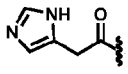
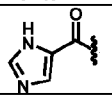
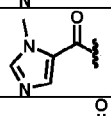
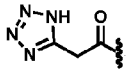
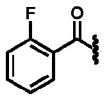
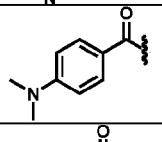
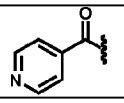
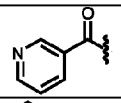
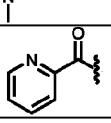
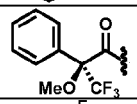
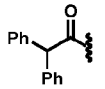
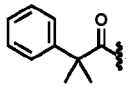
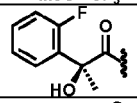
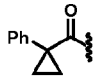
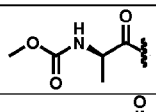
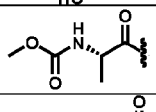
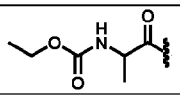
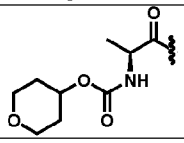
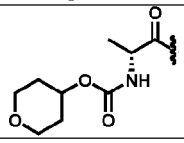
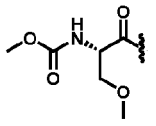
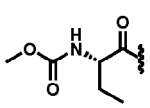
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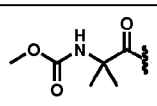
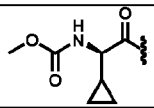
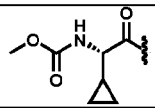
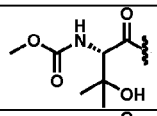
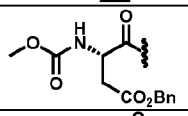
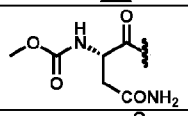
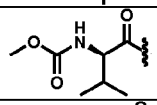
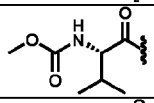
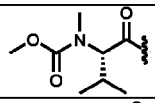
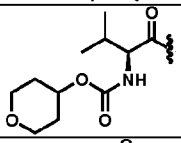
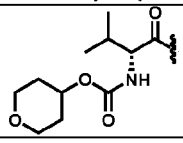
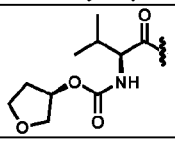
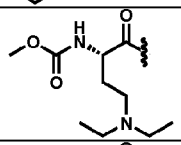
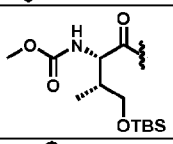
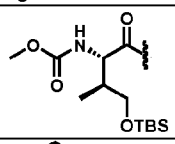
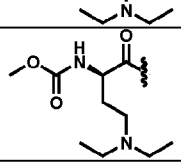
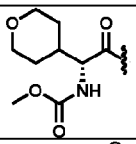
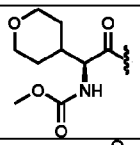
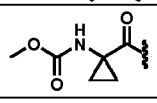
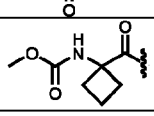
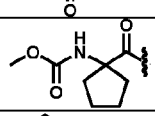
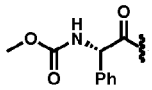
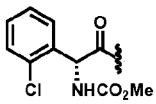
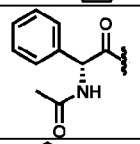
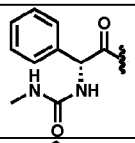
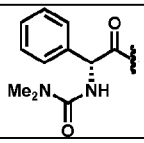
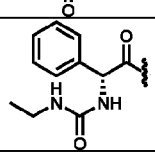
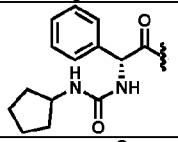
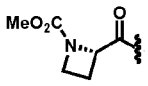
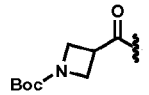
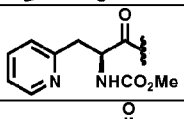
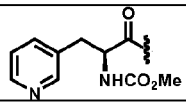
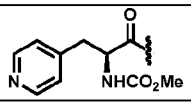
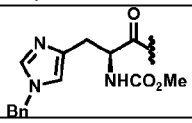
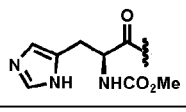
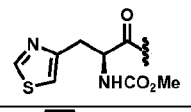
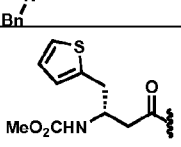
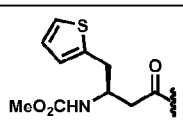
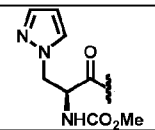
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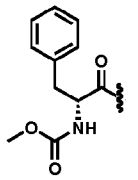
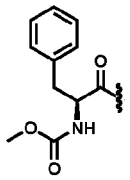
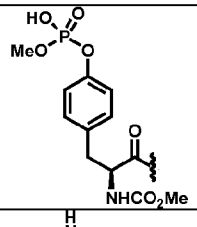
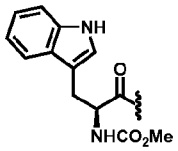
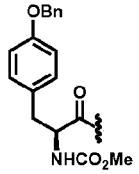
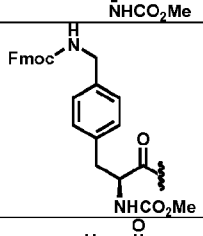
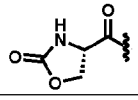
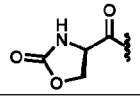
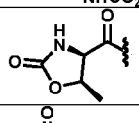
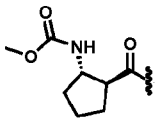
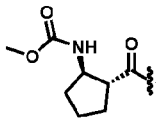
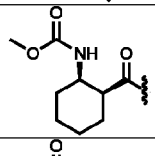
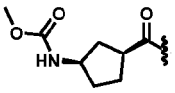
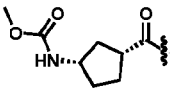
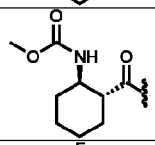
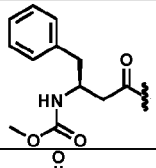
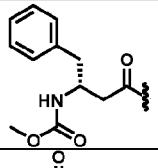
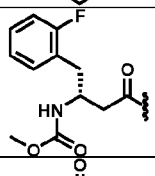
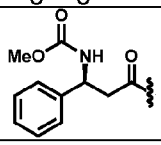
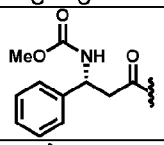
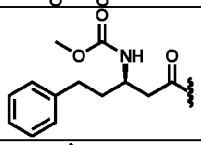
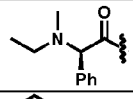
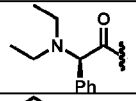
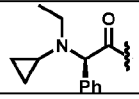
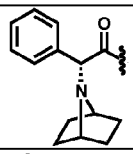
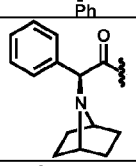
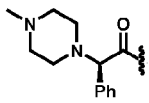
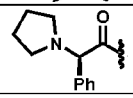
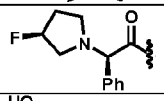
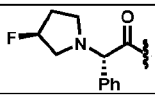
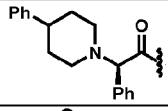
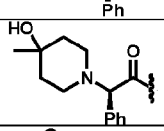
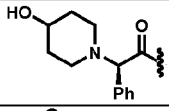
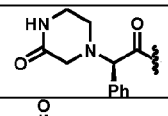
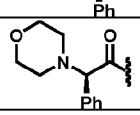
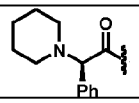
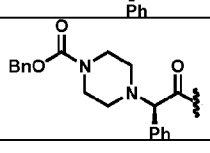
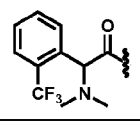
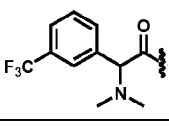
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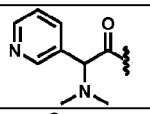
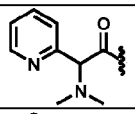
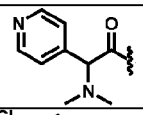
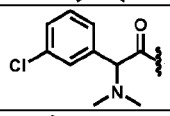
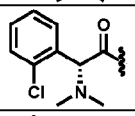
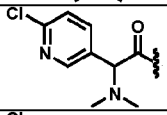
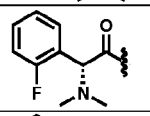
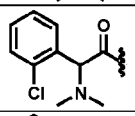
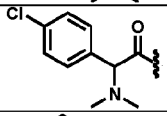
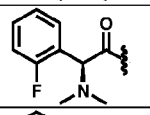
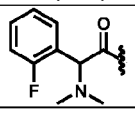
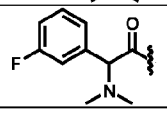
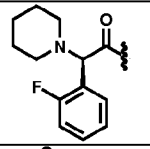
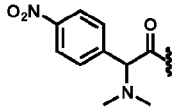
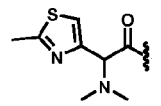
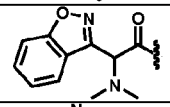
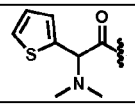
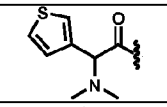
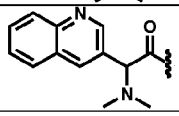
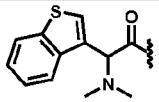
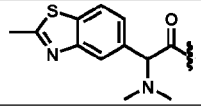
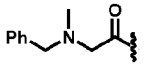
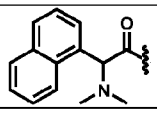
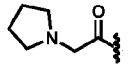
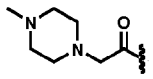
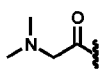
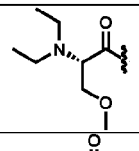
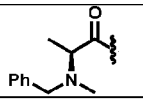
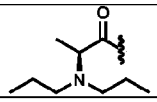
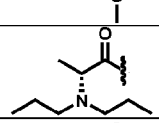
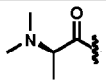
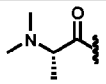
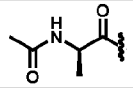
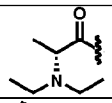
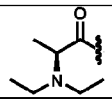
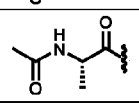
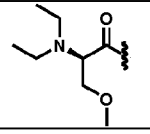
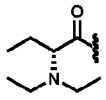
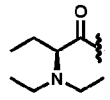
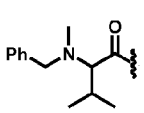


Entry 1-		Entry 1-		Entry 1-	
1		2		3	
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52		53		54	
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64		65		66	
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97		98		99	
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121		122		123	
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151		152		153	
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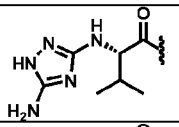
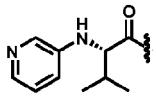
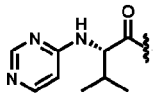
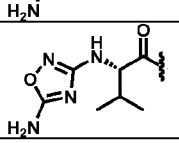
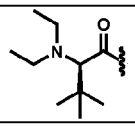
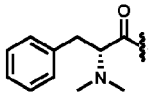
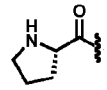
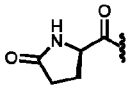
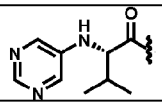
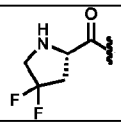
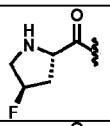
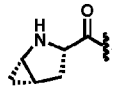
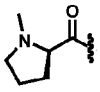
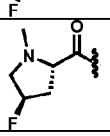
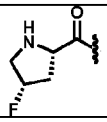
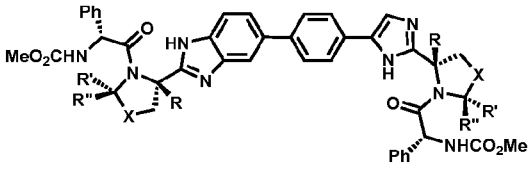
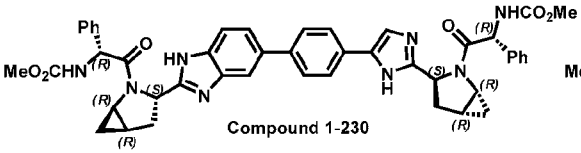
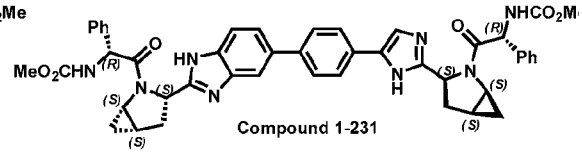
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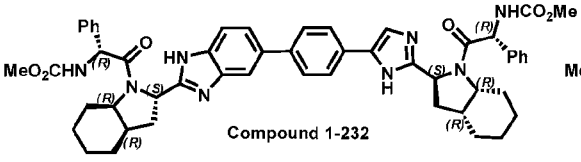
Table 2: Compounds 1-220 to 1-229.



Entry 1-	R	R'	R"	X	Entry 1-	R	R'	R"	X
220	Me	H	H	CH_2	221	H	H	H	CF_2
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH_2	227	H	H	H	
228	H	H	Ph	CH_2	229	H	H	H	







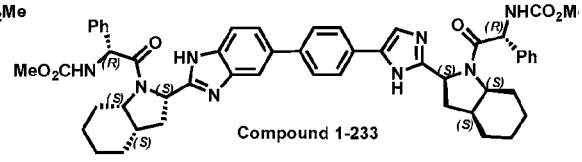
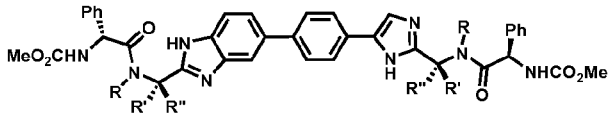
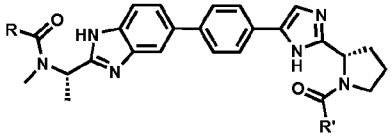


Table 3: Compounds 1-234 to 1-243.



Entry 1-	R	R'	R"	Entry 1-	R	R'	R"
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	$CHMe_2$	H	243	Me	Et	H

Table 4: Compounds 1-244 to 1-263.



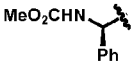
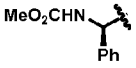
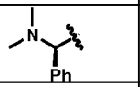
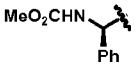
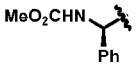
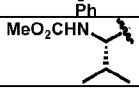
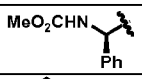
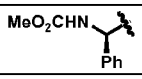
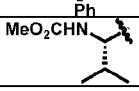
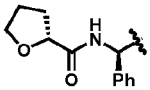
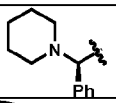
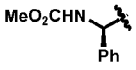
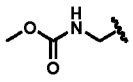
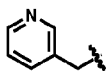
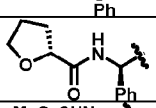
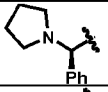
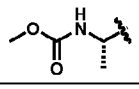
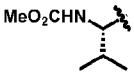
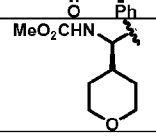
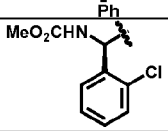
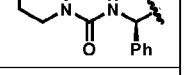
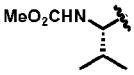
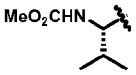
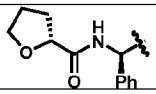
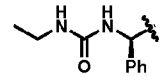
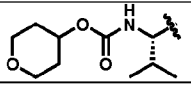
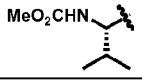
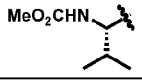
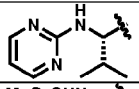
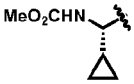
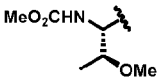
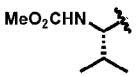
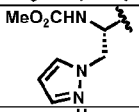
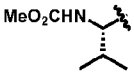
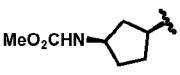
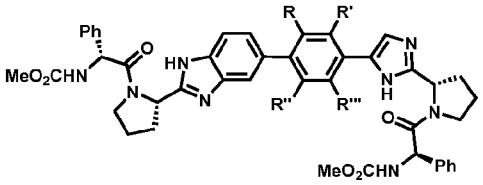
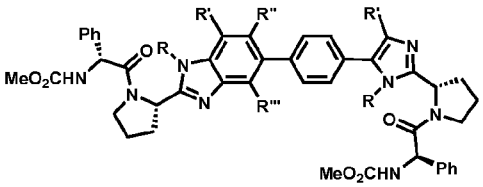
Entry 1-	R	R'	Entry 1-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 5: Compounds 1-264 to 1-273.



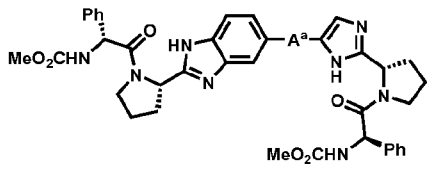
Entry 1-	R	R'	R"	R'"	Entry 1-	R	R'	R"	R'"
264	F	H	H	H	265	F	F	H	H
266	Me	H	H	H	267	Me	Me	H	H
268	H	H	Me	Me	269	H	H	Et	Et
270	CF_3	H	H	H	271	CF_3	H	CF_3	H
272	Cl	H	H	H	273	Cl	H	Cl	H

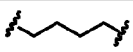
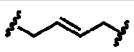
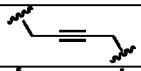
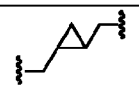
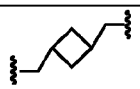
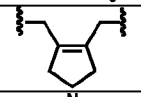
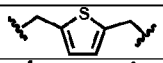
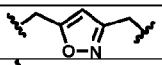
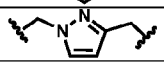
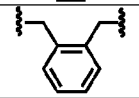
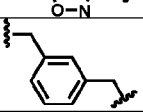
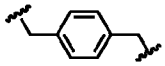
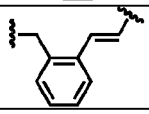
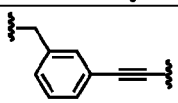
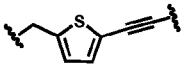
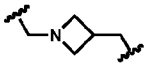
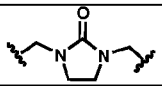
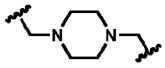
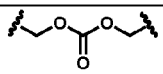
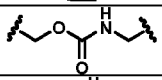
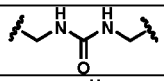
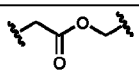
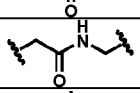
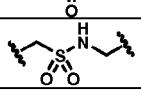
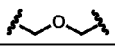
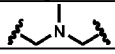
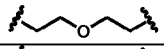
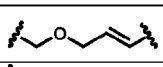
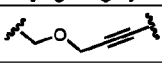
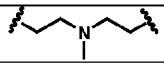
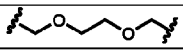
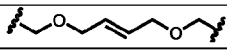
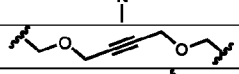
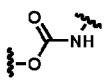
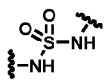
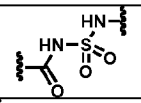
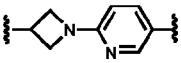
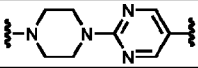
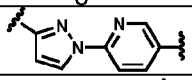
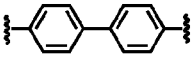
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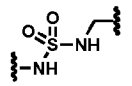
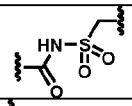
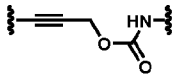
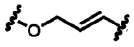
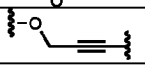
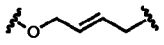
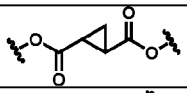
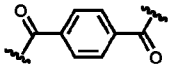
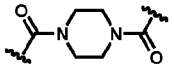
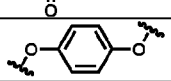
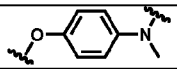
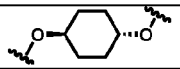
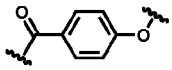
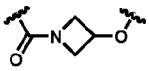
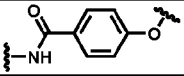
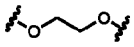
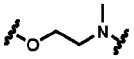
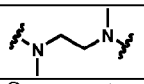
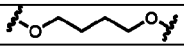
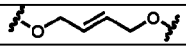
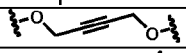
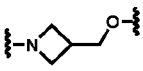
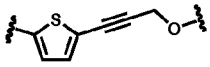
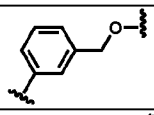
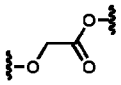
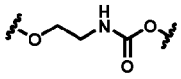
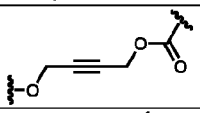
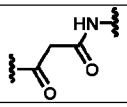
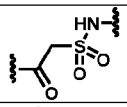
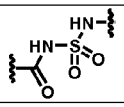
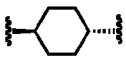
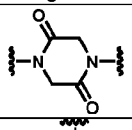
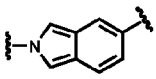
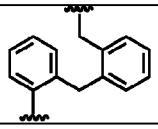
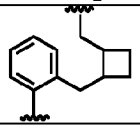
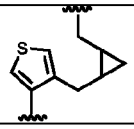
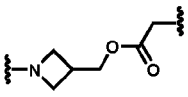
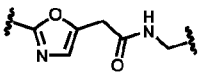
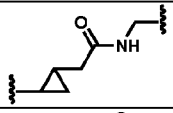
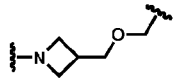


Entry 1-	R	R'	R"	R'"	Entry 1-	R	R'	R"	R'"
274	Me	H	H	H	275	H	CO_2H	H	H
276	H	F	H	H	277	H	H	CO_2H	H
278	H	H	F	H	279	H	H	H	CO_2H
280	H	H	H	F	281	H	CO_2Me	H	H
282	H	Cl	H	H	283	H	H	CO_2Me	H
284	H	H	Cl	H	285	H	H	H	CO_2Me
286	H	H	H	Cl	287	H	$CONH_2$	H	H
288	H	Me	H	H	289	H	H	$CONH_2$	H
290	H	H	Me	H	291	H	H	H	$CONH_2$
292	H	H	H	Me	293	H	OMe	H	H
294	H	CF_3	H	H	295	H	H	OMe	H
296	H	H	CF_3	H	297	H	H	H	OMe
298	H	H	H	CF_3	299	CO_2Me	H	H	H

Table 7: Compounds 1-300 to 1-434.



Entry 1-	A[a]	Entry 1-	A[a]	Entry 1-	A[a]
300		301		302	
303		304		305	
306		307		308	
309		310		311	
312		313		314	
315		316		317	
318		319		320	
321		322		323	
324		325		326	
327		328		329	
330		331		332	
333		334		335	
336		337		338	
339		340		341	
342		343		344	
345		346		347	
348		349		350	
351		352		353	
354		355		356	
357		358		359	
360		361		362	
363		364		365	

366		367		368	
369		370		371	
372		373		374	
375		376		377	
378		379		380	
381		382		383	
384		385		386	
387		388		389	
390		391		392	
393		394		395	
396		397		398	
399		400		401	
402		403		404	
405		406		407	
408		409		410	
411		412		413	
414		415		416	
417		418		419	

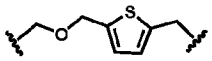
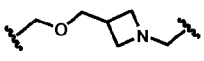
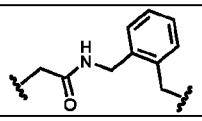
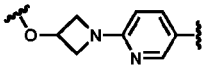
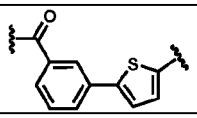
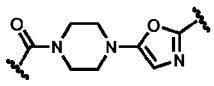
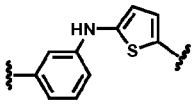
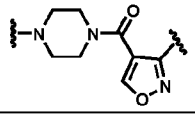
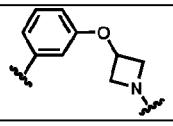
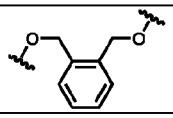
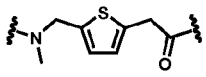
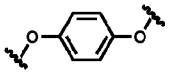
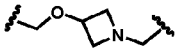
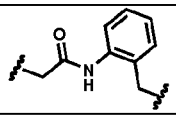
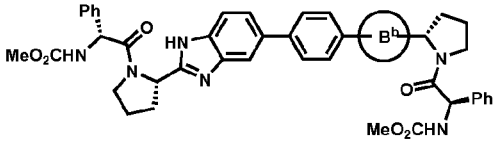
420		421		422	
423		424		425	
426		427		428	
429		430		431	
432		433		434	

Table 8: Compounds 1-435 to 1-440.



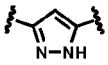
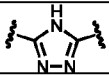
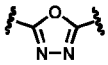
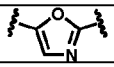
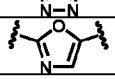
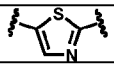
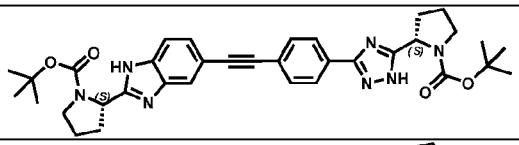
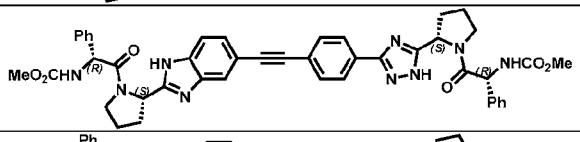
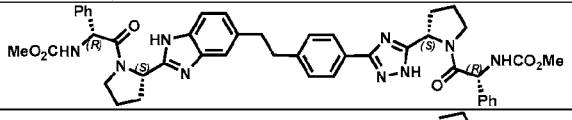
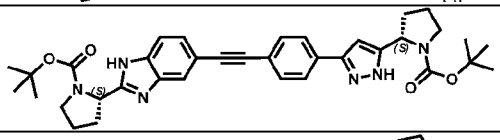
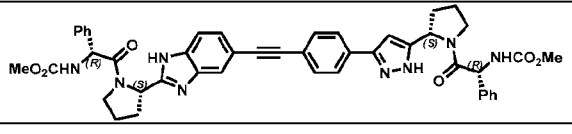
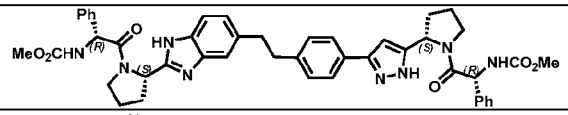
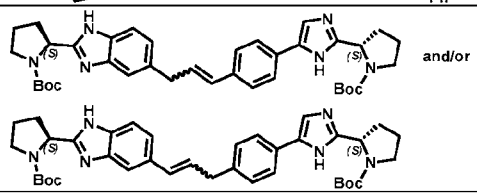
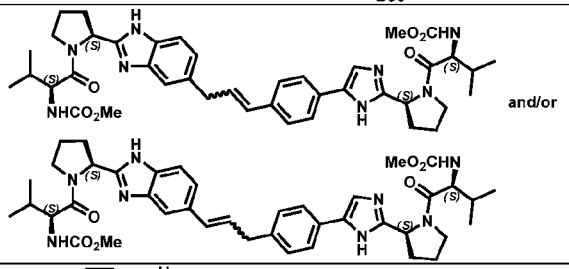
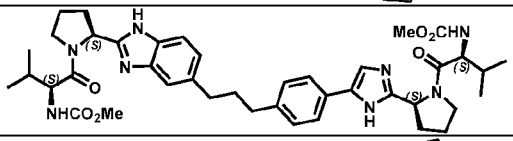
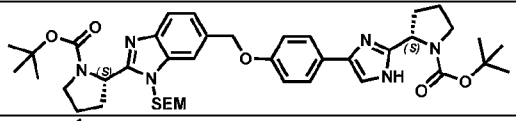
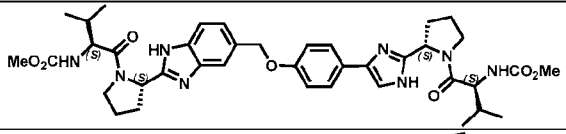
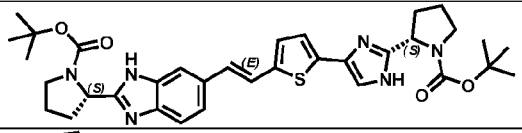
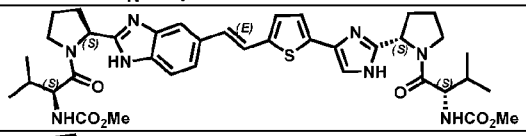
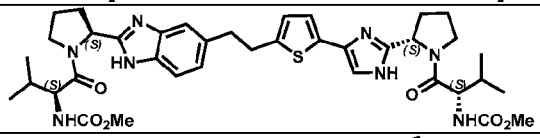
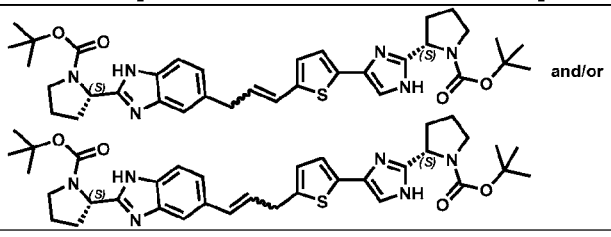
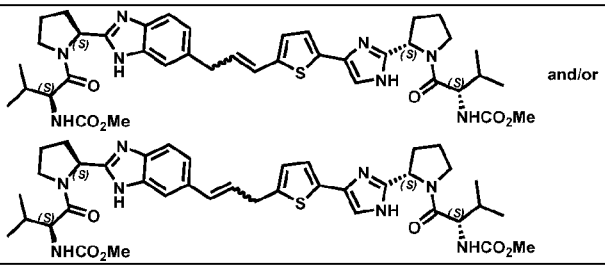
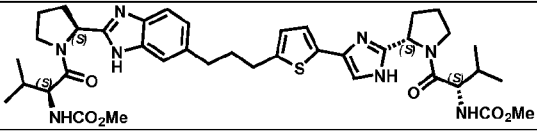
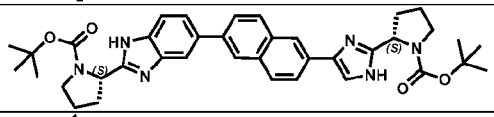
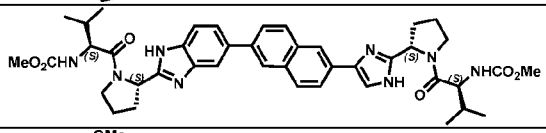
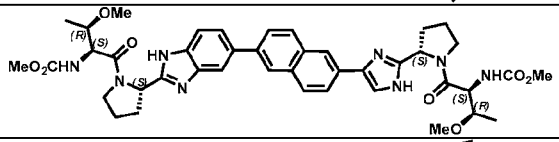
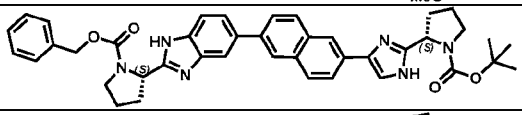
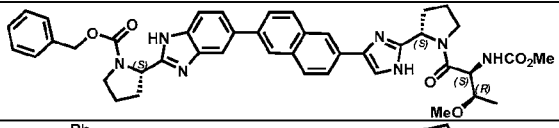
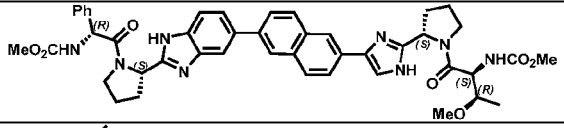
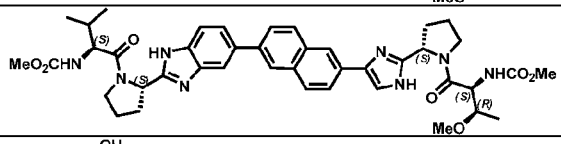
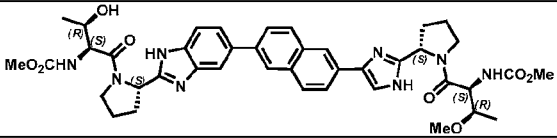
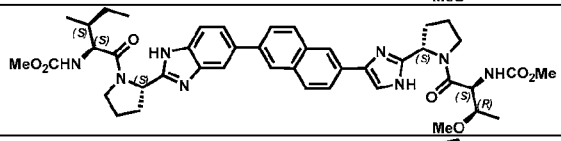
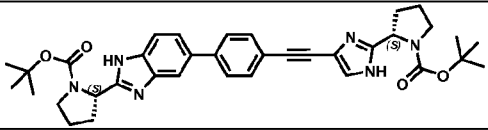
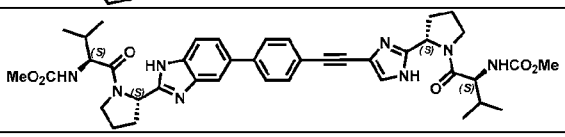
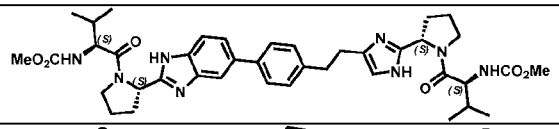
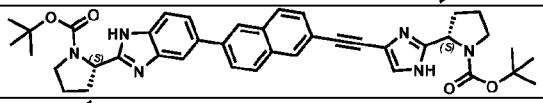
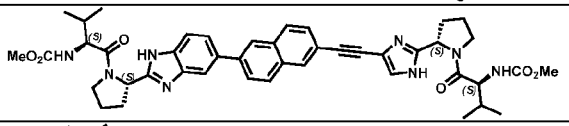
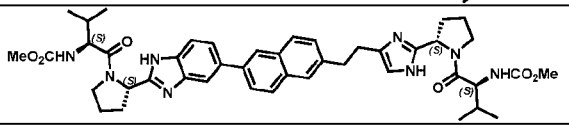
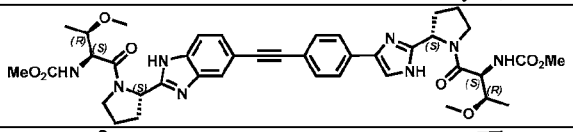
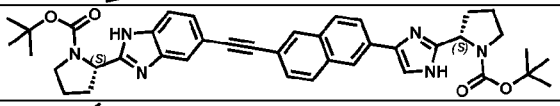
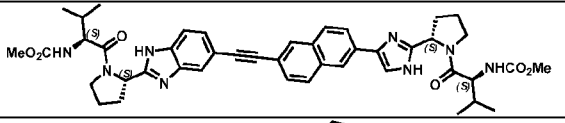
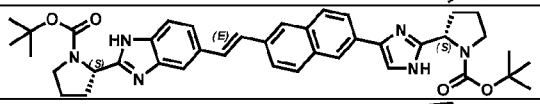
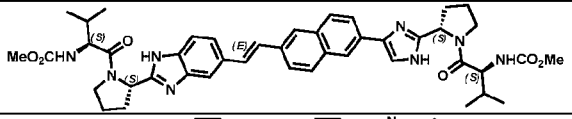
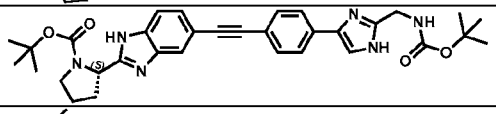
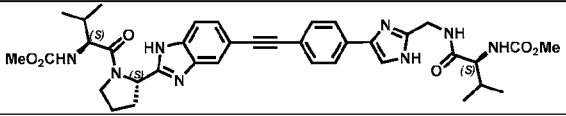
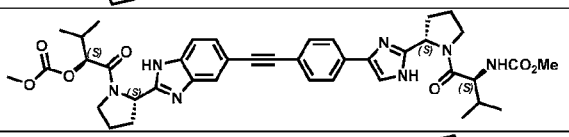
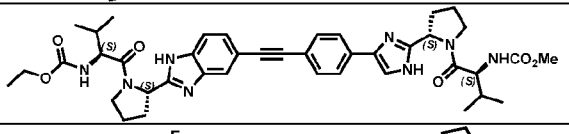
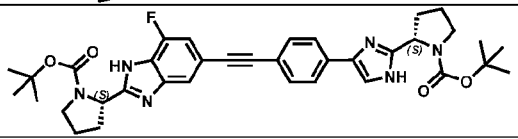
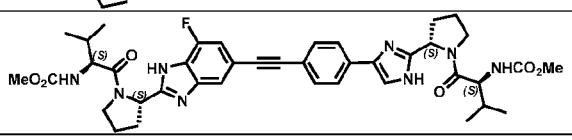
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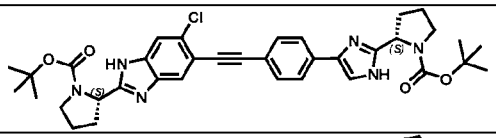
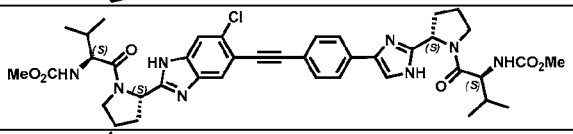
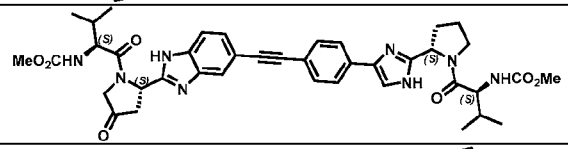
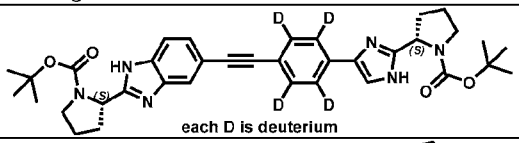
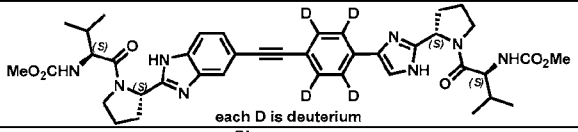
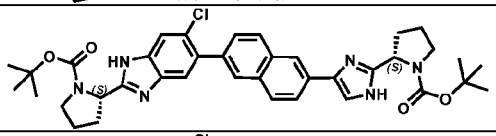
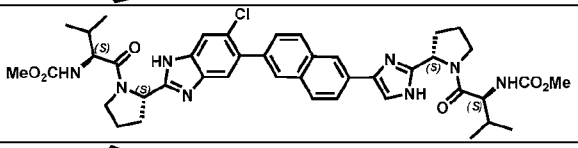
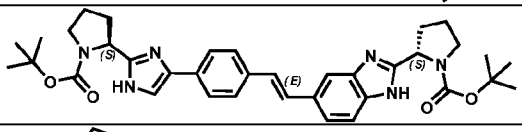
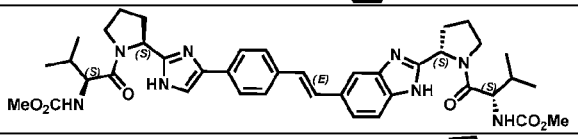
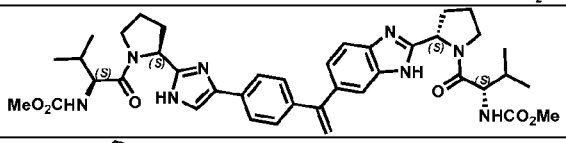
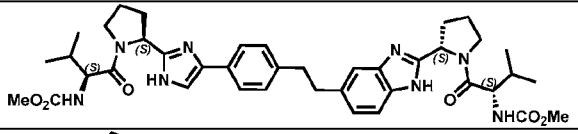
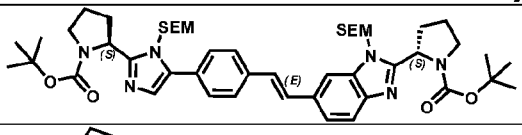
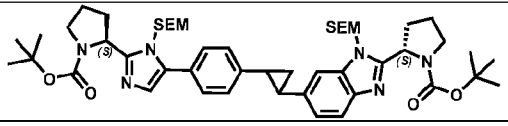
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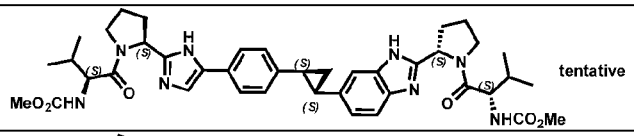
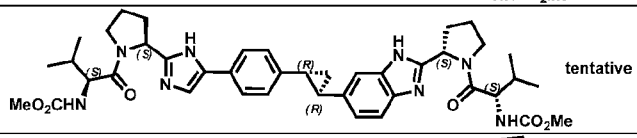
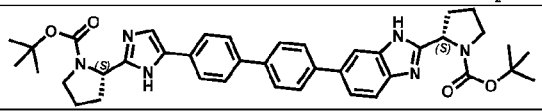
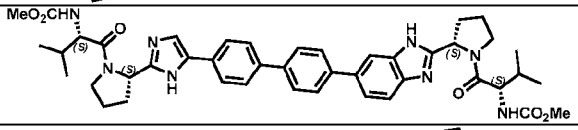
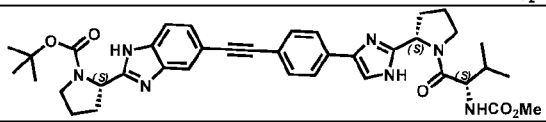
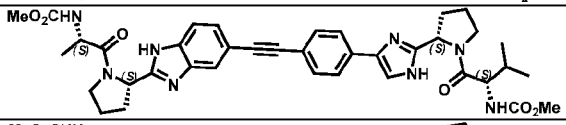
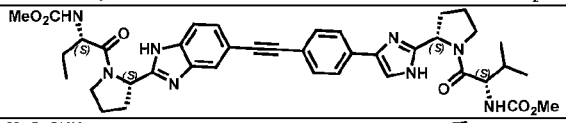
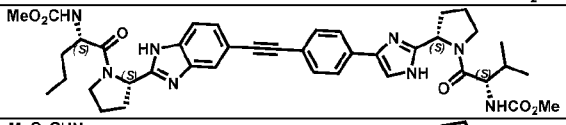
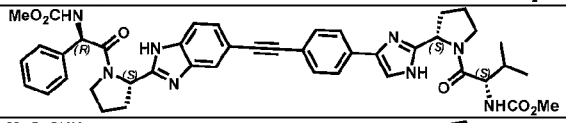
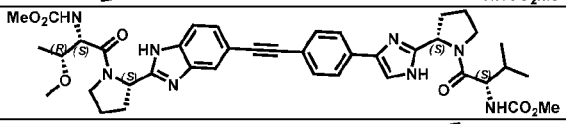
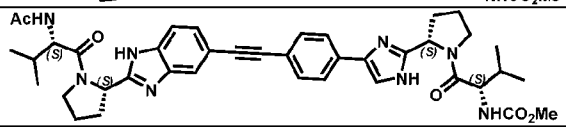
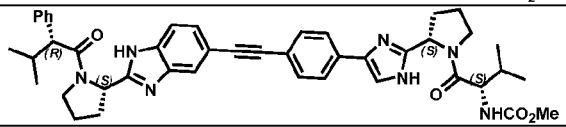
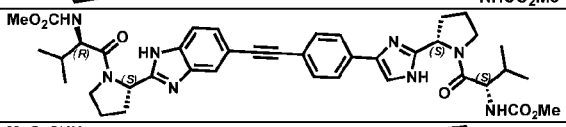
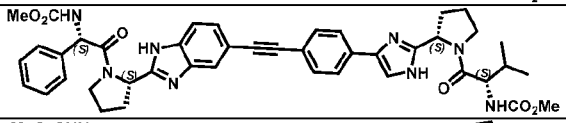
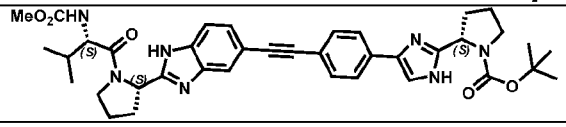
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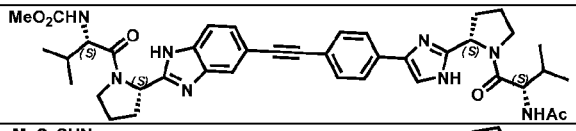
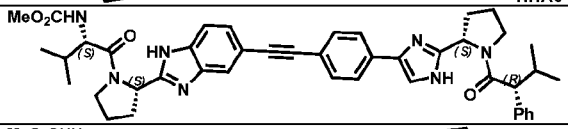
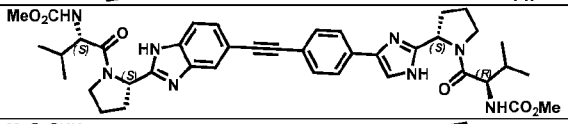
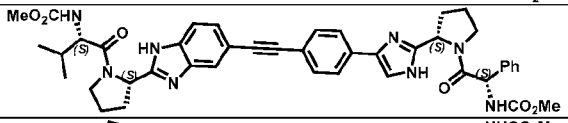
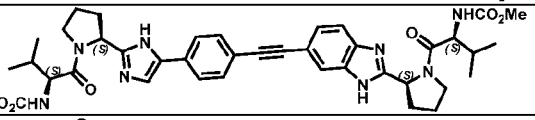
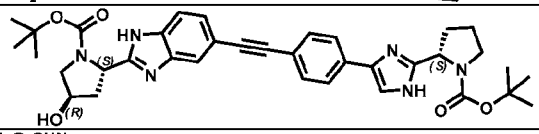
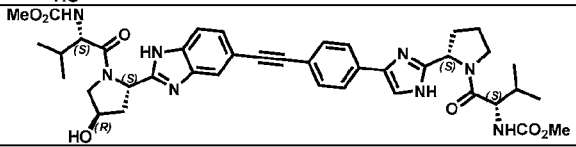
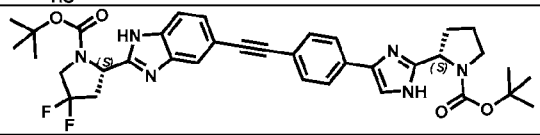
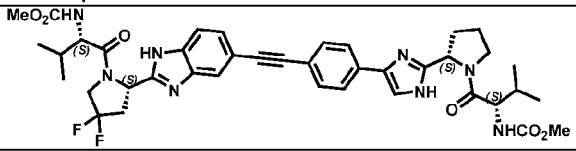
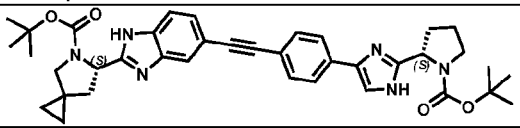
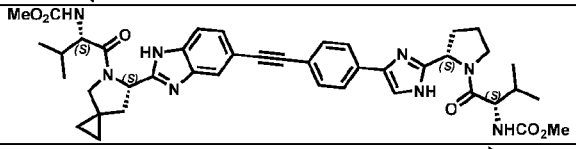
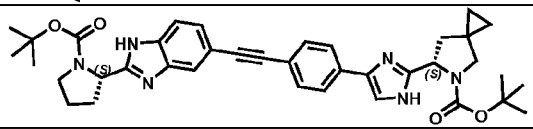
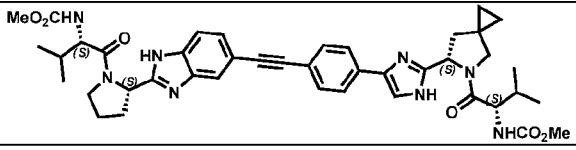
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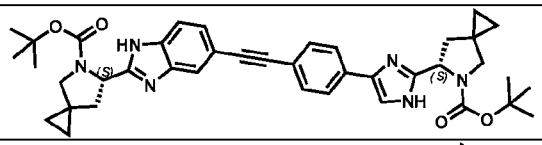
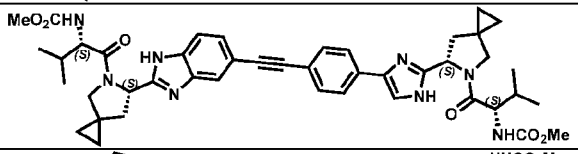
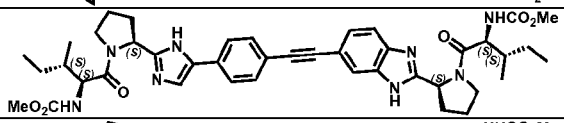
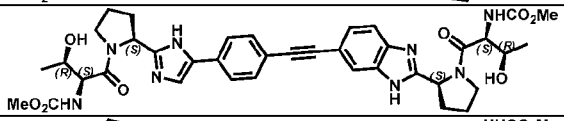
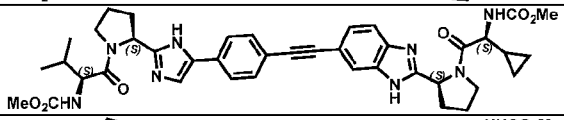
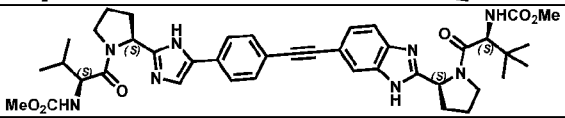
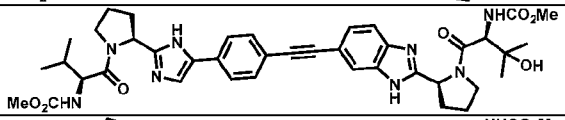
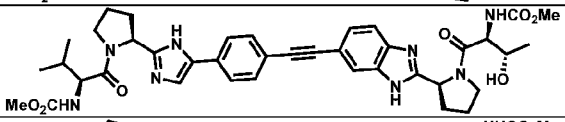
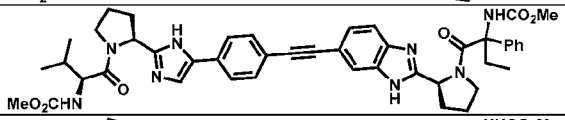
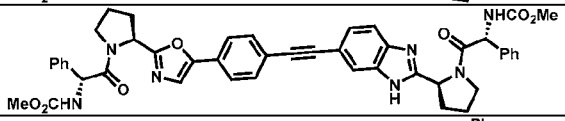
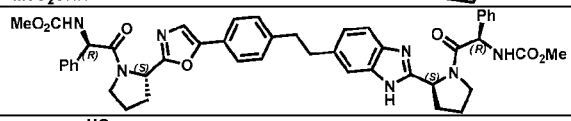
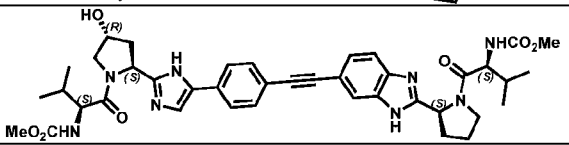
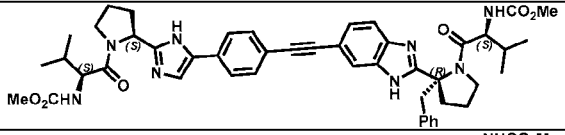
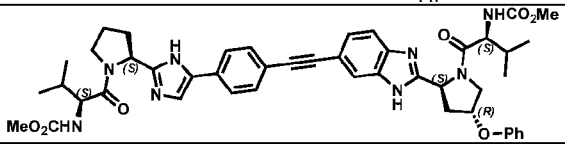
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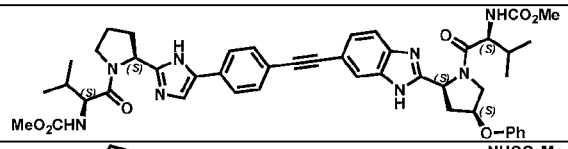
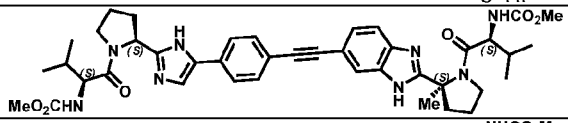
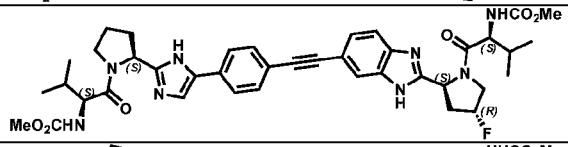
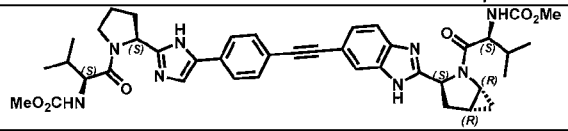
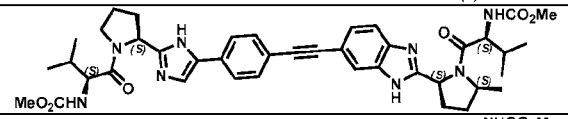
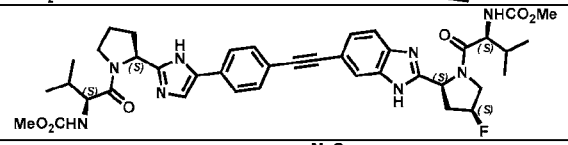
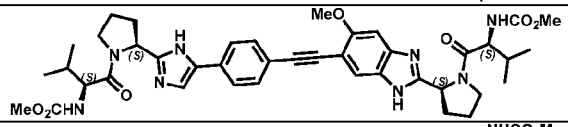
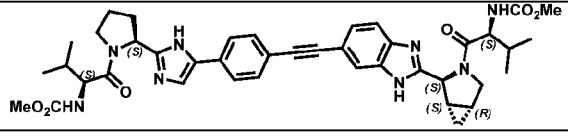
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II. Compounds having the Formula (**2-I**)

The present invention relates to compounds of Formula (**2-I**) as illustrated above, or a pharmaceutically acceptable salt thereof.

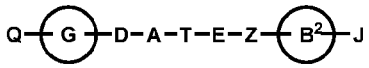
In one embodiment, the present invention relates to compounds of Formula (**2-Ia**), or a pharmaceutically acceptable salt thereof:



(2-Ia)

wherein A, D, E, Ring G, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring B^1 is an optionally substituted five-membered heteroaryl; and Ring B^1 is C-attached to J and one of Z, E, T, A and D. In some aspects, Ring B^1 is an optionally substituted five-membered heteroaryl that contains one or more nitrogen atoms.

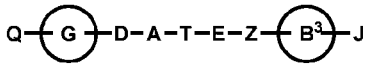
In another embodiment, the present invention relates to compounds of Formula (**2-Iaa**), or a pharmaceutically acceptable salt thereof:



(2-Iaa)

wherein A, D, E, Ring G, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring B^2 is selected from imidazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiazolyl, and isoxazolyl; and Ring B^2 is C-attached to each of J and one of Z, E, T, A and D.

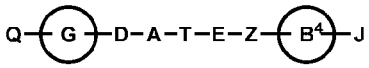
In yet another embodiment, the present invention relates to compounds of Formula (**2-Ib**), or a pharmaceutically acceptable salt thereof:



(2-Ib)

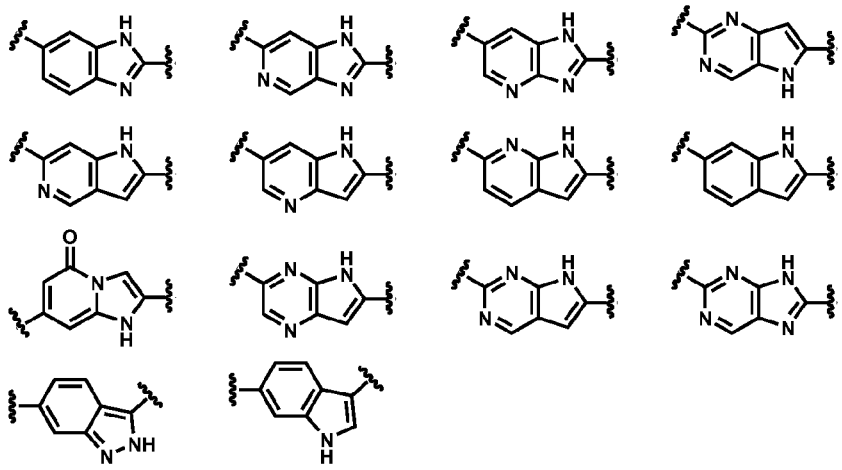
wherein A, D, E, Ring G, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring B^3 is an optionally substituted 5/6 fused heteroaryl, wherein the 6-membered ring of said 5/6-fused heteroaryl is C-attached to one of groups Z, E, T, A and D, and the 5-membered ring is C-attached to group J and containing one or more nitrogen atoms.

In still another embodiment, the present invention relates to compounds of Formula (**2-Ibb**), or a pharmaceutically acceptable salt thereof:



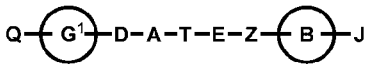
(2-Ibb)

wherein A, D, E, Ring G, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring B^4 is selected from the group consisting of:



.

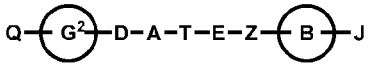
In yet another embodiment, the present invention relates to compounds of Formula (**2-Ic**), or a pharmaceutically acceptable salt thereof:



(2-Ic)

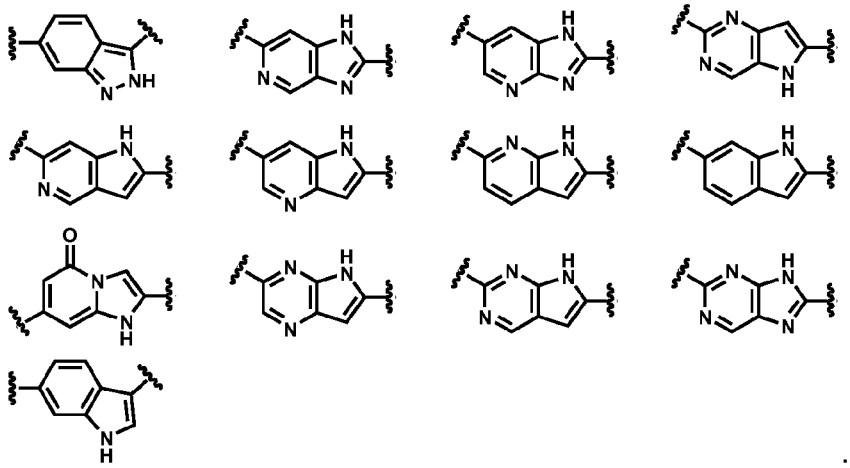
wherein A, Ring B, D, E, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring G^1 is an optionally substituted 5/6 fused heteroaryl other than benzimidazolyl, with the 6-membered ring C-attached to one of groups D, A, T, E and Z and the 5-membered ring C-attached to group J and containing one or more nitrogen atoms.

In still another embodiment, the present invention relates to compounds of Formula (**2-Icc**), or a pharmaceutically acceptable salt thereof:

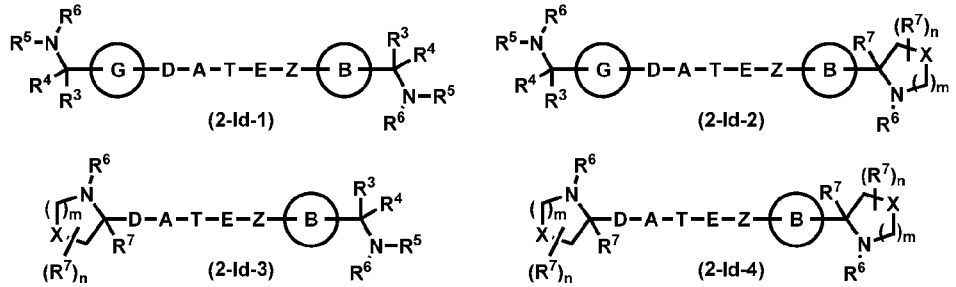


(2-Icc)

wherein A, Ring B, D, E, T, Z, Q, and J are as previously defined in Formula (**2-I**) and Ring G^2 is selected from the group consisting of:



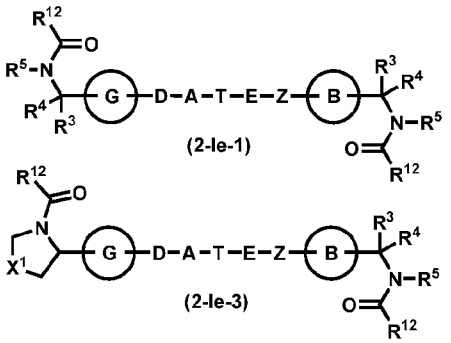
In still another embodiment, the present invention relates to compounds of Formulae (**2-Id-1** to **2-Id-4**), or a pharmaceutically acceptable salt thereof:

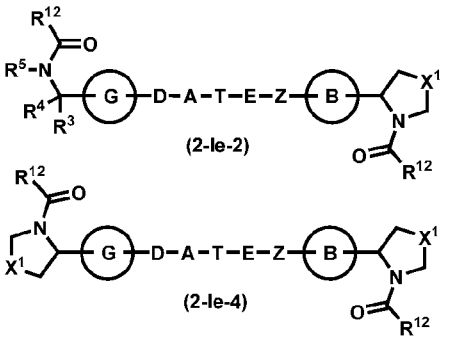


(2-Id-1) (2-Id-2) (2-Id-3) (2-Id-4)

wherein A, D, E, Ring B, Ring G, T, Z, X, m, n, R^3, R^4, R^5, R^6 and R^7 are as previously defined in Formula (**2-I**).

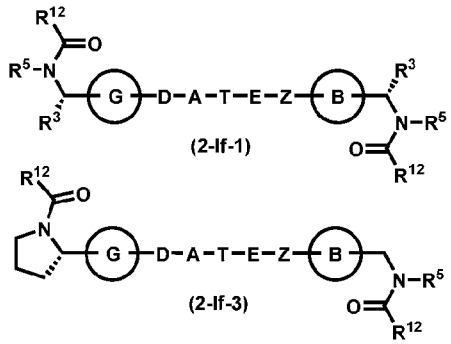
In still another embodiment, the present invention relates to compounds of Formulae (**2-Ie-1** to **2-Ie-4**), or a pharmaceutically acceptable salt thereof:

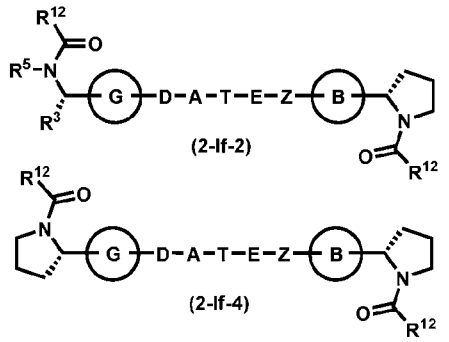




wherein A, Ring B, D, E, Ring G, T, Z, R^3, R^4, R^5, and R^{12} are as previously defined in Formula (**2-I**) and X^1 is independently CH_2, CHF, CH(OH), or CF_2.

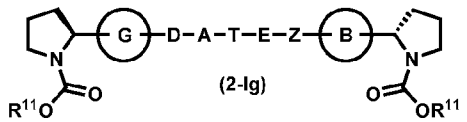
In still another embodiment of the present invention, the absolute stereochemistry of the pyrrolidine and 2-benzimidazolylmethylamine or five-membered heteroarylmethylamine moiety is represented by Formulae (**2-If-1** to **2-If-4**):





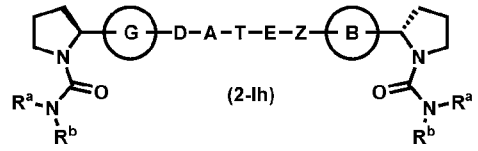
wherein A, B, D, E, G, T, Z, R^3, R^5, and R^{12} are as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-Ig**), or a pharmaceutically acceptable salt thereof:



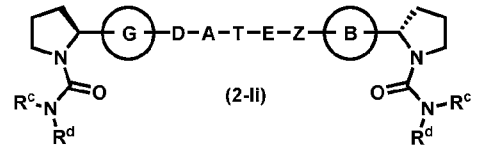
wherein A, D, E, T, Z, Ring B, Ring G and R^{11} are as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-Ih**), or a pharmaceutically acceptable salt thereof:



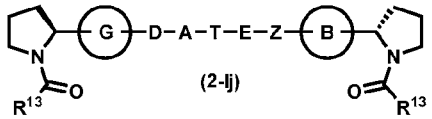
wherein A, Ring B, D, E, Ring G, T, Z, R^a and R^b are as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-Ii**), or a pharmaceutically acceptable salt thereof:



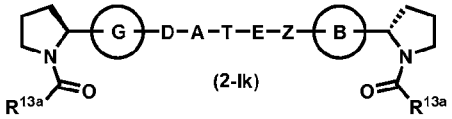
wherein A, Ring B, D, E, Ring G, T, Z, R^c and R^d are as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-Ij**), or a pharmaceutically acceptable salt thereof:



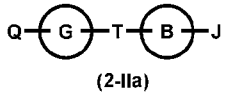
wherein A, Ring B, D, E, Ring G, T, Z, and R^{13} are as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-Ik**), or a pharmaceutically acceptable salt thereof:



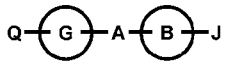
wherein A, Ring B, D, E, Ring G, T, and Z are as previously defined in Formula (**2-I**) and R^{13a} at each occurrence is independently an optionally substituted C_1-C_8 alkyl; preferably C_1-C_8 alkyl optionally substituted with amino, hydroxy, phenyl, protected amino, or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formula (**2-IIa**), or a pharmaceutically acceptable salt thereof:



wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**) and T is present and as previously defined in Formula (**2-I**).

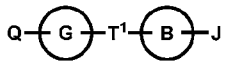
In still another embodiment, the present invention relates to compounds of Formula (**2-IIb**), or a pharmaceutically acceptable salt thereof:



(2-IIb)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**) and A is present and as previously defined in Formula (**2-I**).

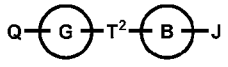
In still another embodiment, the present invention relates to compounds of Formula (**2-IIc**), or a pharmaceutically acceptable salt thereof:



(2-IIc)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**) and T^1 is a linear aliphatic group, optionally comprising one or more of an olefinic double bond, an alkynic triple bond, O, $N(R^{11})$, C(O), $S(O)_2$, C(O)O, $C(O)N(R^{11})$, OC(O)O, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$.

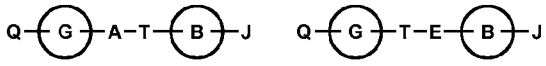
In still another embodiment, the present invention relates to compounds of Formula (**2-IId**), or a pharmaceutically acceptable salt thereof:



(2-IId)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**) and T^2 is an aliphatic group comprising a C_3-C_8 cycloalkyl or C_3-C_8 cycloalkenyl and optionally comprising one or more of an olefinic double bond, an alkynic triple bond, O, $N(R^{11})$, C(O), $S(O)_2$, C(O)O, $C(O)N(R^{11})$, OC(O)O, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $C(O)N(R^{11})S(O)_2$ and $C(O)N(R^{11})S(O)_2N(R^{11})$.

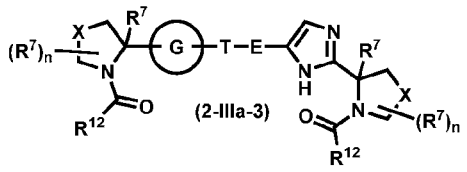
In still another embodiment, the present invention relates to compounds of Formulae (**2-IIIa-1** and **2-IIIa-2**), or a pharmaceutically acceptable salt thereof:



(2-IIIa-1) (2-IIIa-2)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**); in Formula (**2-IIIa-1**), A and T are each present and as previously defined in Formula (**2-I**); and in Formula (**2-IIIa-2**), T and E are each present and as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-IIIa-3**), or a pharmaceutically acceptable salt thereof:

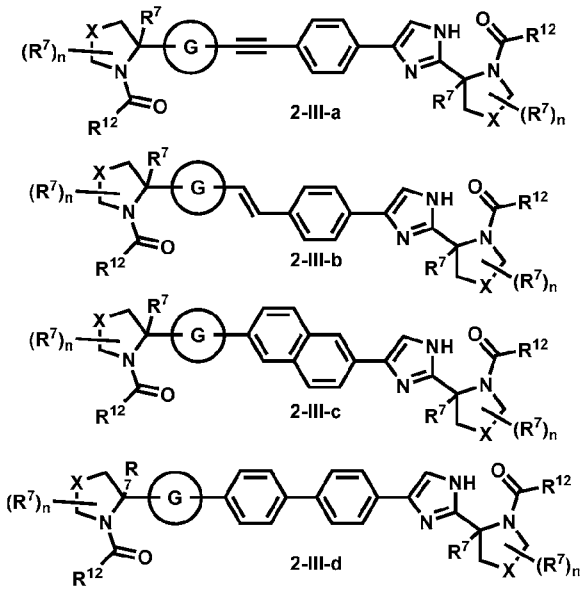


wherein Ring G is as previously defined in Formula (**2-I**); n is 1 or 2; T is absent or optionally substituted C_2-C_4 alkenyl or optionally substituted C_2-C_4 alkynyl; E is phenyl, monocyclic heteroaryl, bicyclic aryl, or bicyclic heteroaryl, each optionally substituted; X at each occurrence is independently CH_2, CHF, CH(OH), CHMe, CF_2, or $C(R^7)_2$; wherein R^7 at each occurrence is independently hydrogen or methyl; alternatively, two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro, optionally substituted C_3-C_8 cycloalkyl; or yet alternatively, two vicinal R^7 groups can be taken together with the two adjacent atoms to which they are attached to form a fused, optionally substituted C_3-C_8 cycloalkyl; and R^{12} at each occurrence is independently optionally substituted C_1-C_8 alkyl.

In still another embodiment, the present invention relates to compounds of Formula (**2-IIIa-3**), or a pharmaceutically acceptable salt thereof; wherein two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formula (**2-IIIa-3**), or a pharmaceutically acceptable salt thereof; wherein two vicinal R^7 groups can be taken together with the two adjacent atoms to which they are attached to form a fused cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formulae (**2-III-a**) to (**2-III-d**), or a pharmaceutically acceptable salt thereof:



2-III-a

2-III-b

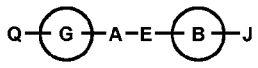
2-III-c

2-III-d

wherein Ring G is imidazolpyridyl; n is 1 or 2; X at each occurrence is each independently CH_2, CHF, CH(OH), CHMe, CF_2, or $C(R^7)_2$; wherein R^7 at each occurrence is independently hydrogen or methyl; alternatively, two geminal R^7 groups are taken together with the carbon to which they are attached to form a spiro cyclopropyl; or yet alternatively, two vicinal R^7 groups can be taken together with the two adjacent atoms to which they are attached to form a fused cyclopropyl; and R^{12} at each occurrence is independently C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or O(C_1-C_4 alkyl).

In still another embodiment, the present invention relates to compounds of Formulae (**2-III-a**) to (**2-III-d**); wherein R^{12} at each occurrence is independently C_1-C_8 alkyl substituted with -$NHCO_2$(C_1-C_4 alkyl) or O(C_1-C_4 alkyl); or a pharmaceutically acceptable salt thereof.

In still another embodiment, the present invention relates to compounds of Formula (**2-IIIb**), or a pharmaceutically acceptable salt thereof:



(2-IIIb)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**); A and E are each present and as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formulae (**2-IVa-1** and **2-IVa-2**), or a pharmaceutically acceptable salt thereof:



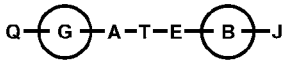
(2-IVa-1)



(2-IVa-2)

wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**); in Formula (**2-IVa-1**), D, A, and T are each present and as previously defined in Formula (**2-I**); and in Formula (**2-IVa-2**), E, T, and Z are each present and as previously defined in Formula (**2-I**).

In still another embodiment, the present invention relates to compounds of Formula (**2-IVb**), or a pharmaceutically acceptable salt thereof:



(2-IVb)

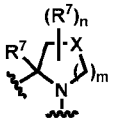
wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**); A, E, and T are each present and as previously defined in Formula (**2-I**).

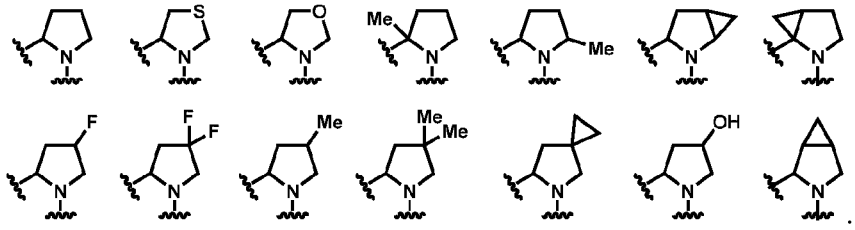
In still another embodiment, the present invention relates to compounds of Formulae (**2-Va-1** and **2-Va-2**), or a pharmaceutically acceptable salt thereof:



(2-Va-1) (2-Va-2)

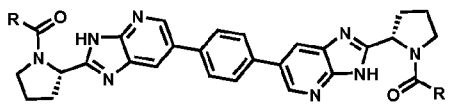
wherein Q, J, Ring B, and Ring G are as previously defined in Formula (**2-I**); in Formula (**2-Va-1**), D, A, T and E are each present and as previously defiend in Formula (**2-I**); and in Formula (**2-Va-2**), A, E, T, and Z are each present and as previously defined in Formula (**2-I**).

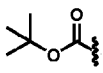
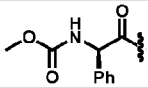
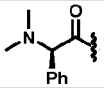
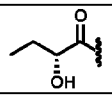
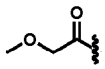
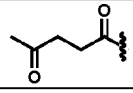
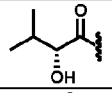
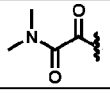
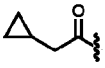
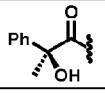
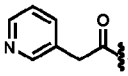
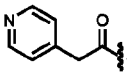
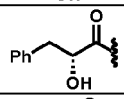
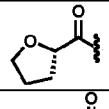
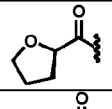
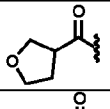
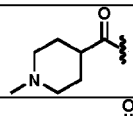
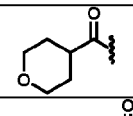
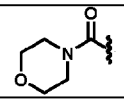
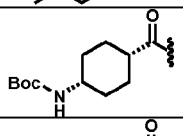
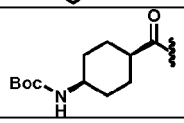
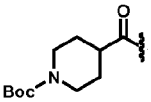
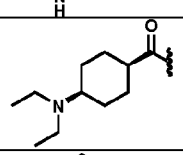
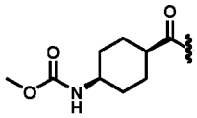
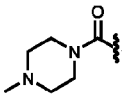
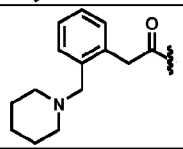
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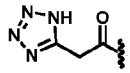
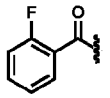
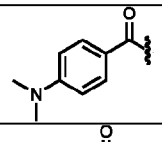
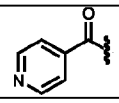
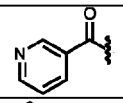
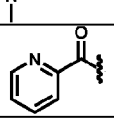
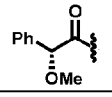
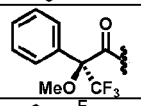
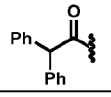
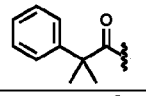
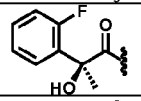
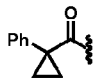
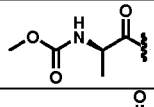
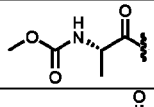
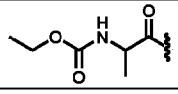
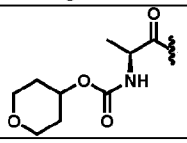
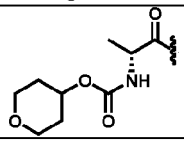
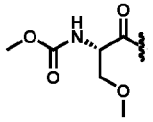
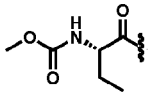
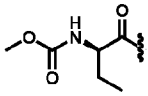
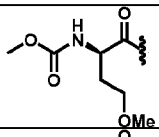
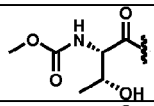
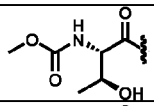
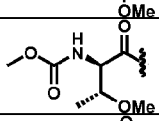
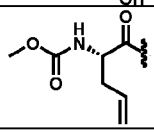
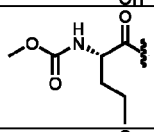
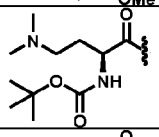
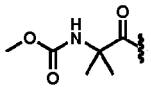
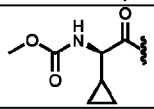
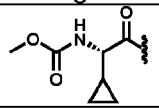
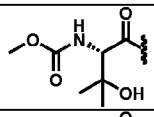
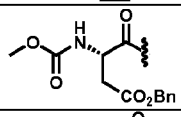
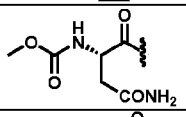
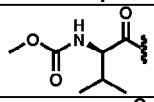
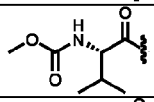
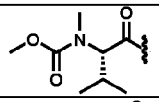
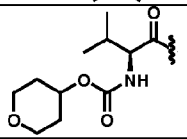
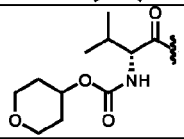
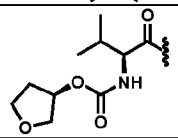
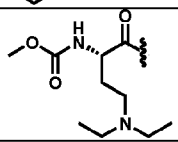


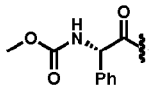
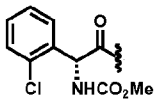
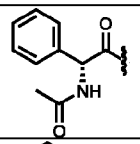
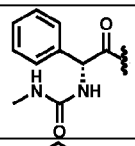
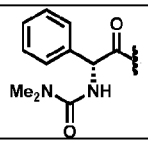
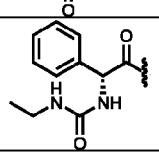
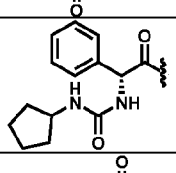
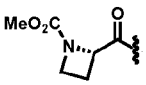
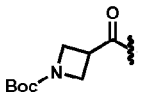
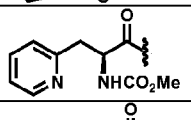
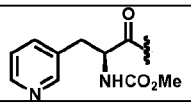
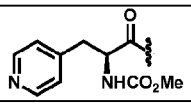
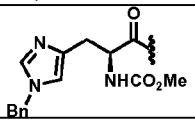
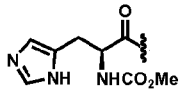
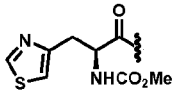
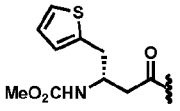
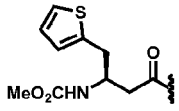
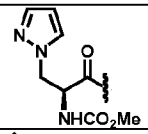
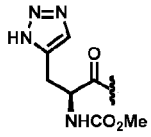
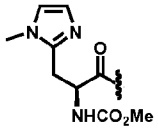
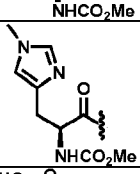
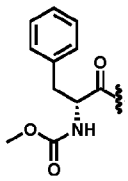
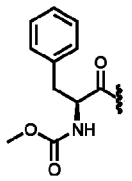
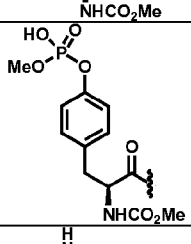
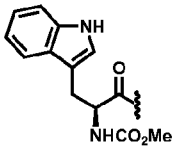
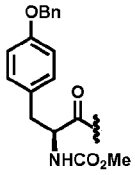
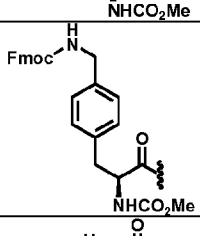
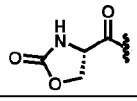
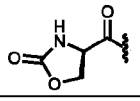
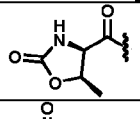
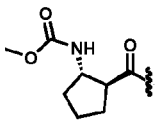
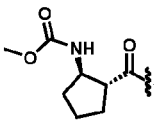
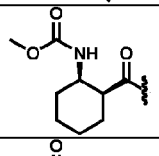
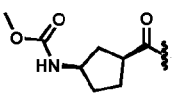
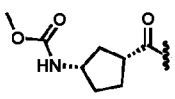
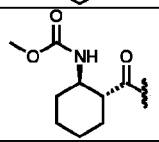
Representative compounds of the present invention are those selected from compounds 2-1 to 2-516 compiled in Tables 10-20:

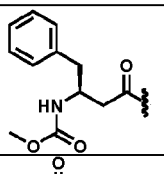
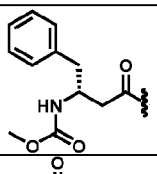
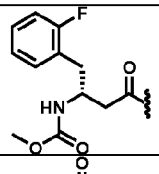
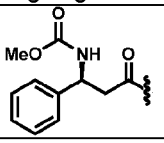
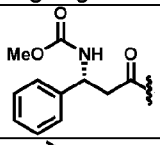
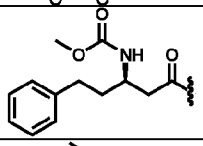
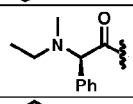
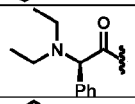
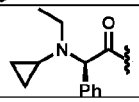
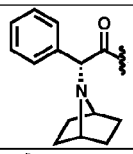
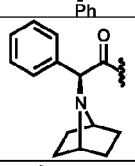
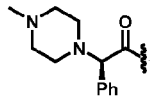
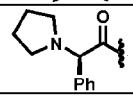
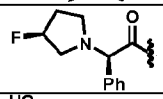
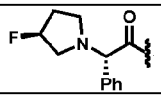
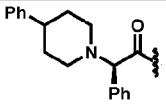
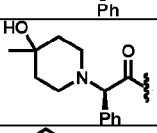
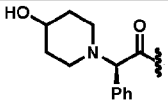
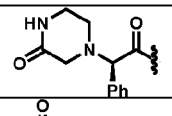
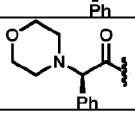
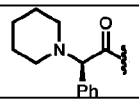
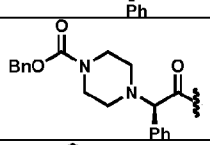
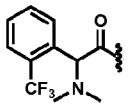
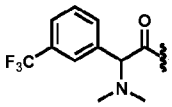
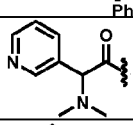
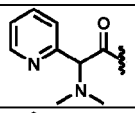
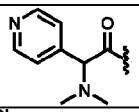
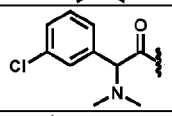
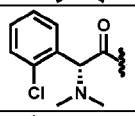
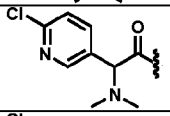
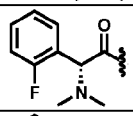
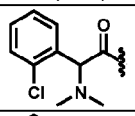
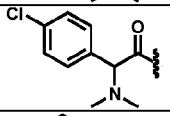
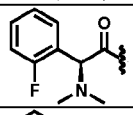
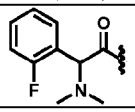
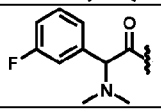
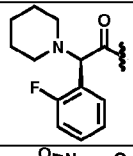
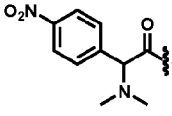
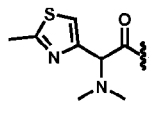
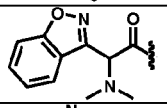
Table 10: Compounds 2-1 to 2-219.



Entry 2-		Entry 2-		Entry 2-	
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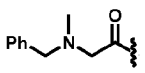
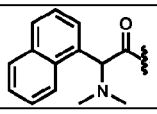
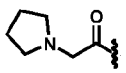
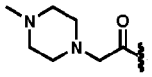
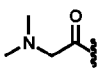
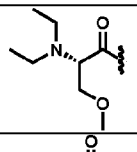
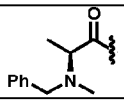
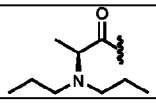
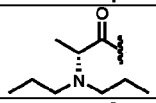
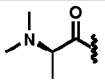
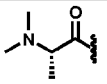
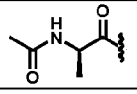
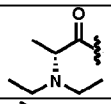
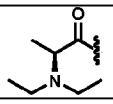
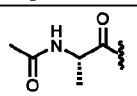
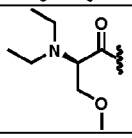
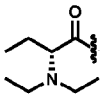
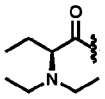
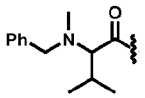
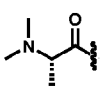
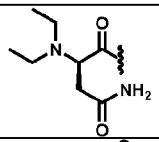
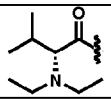
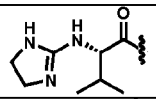
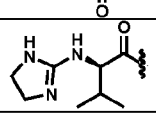
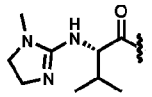
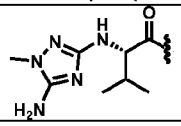
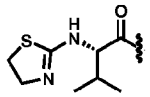
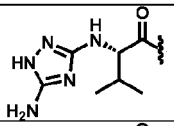
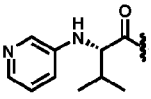
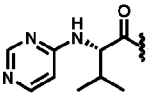
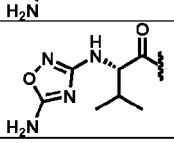
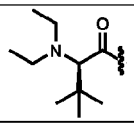
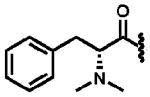
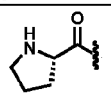
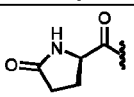
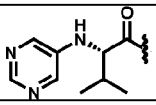
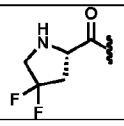
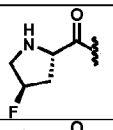
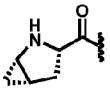
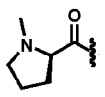
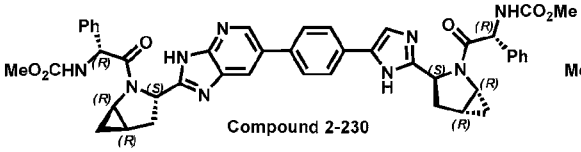
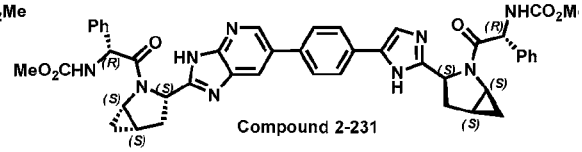
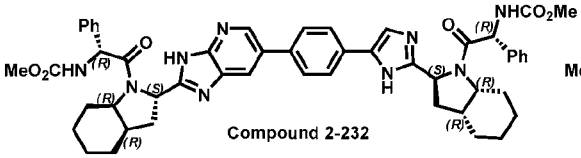
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196		197		198	
199		200		201	
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	

Table 11: Compounds 2-220 to 2-229.

Entry 2-	R	R'	R"	X	Entry 2-	R	R'	R"	X
220	Me	H	H	CH_2	221	H	H	H	CF_2
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH_2	227	H	H	H	
228	H	H	Ph	CH_2	229	H	H	H	







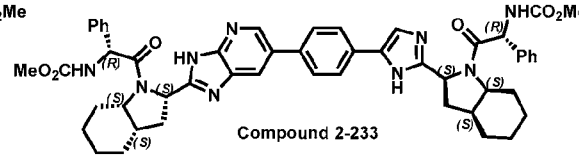
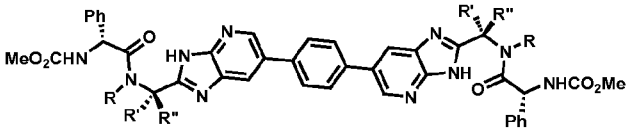
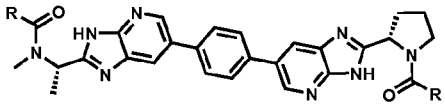


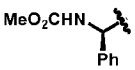
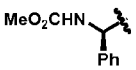
Table 12: Compounds 2-234 to 2-243.



Entry 2-	R	R'	R"	Entry 2-	R	R'	R"
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	$CHMe_2$	H	243	Me	Et	H

Table 13: Compounds 2-244 to 2-263.



Entry 2-	R	R'	Entry 2-	R	R'
244			245		

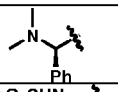
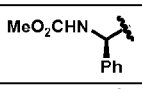
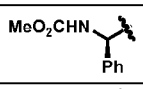
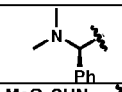
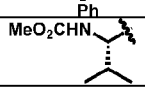
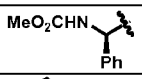
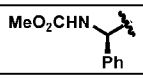
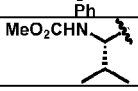
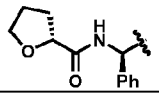
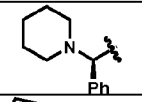
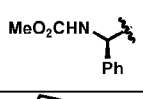
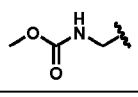
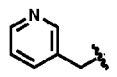
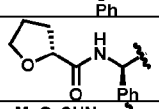
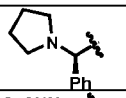
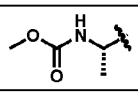
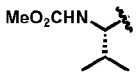
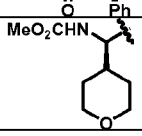
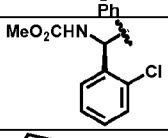
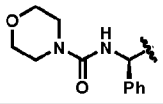
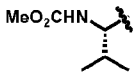
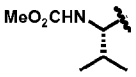
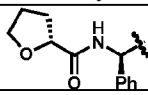
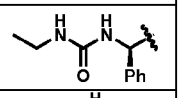
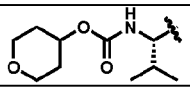
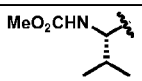
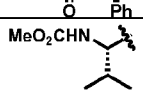
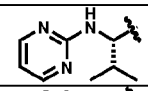
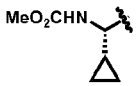
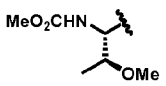
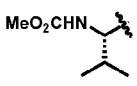
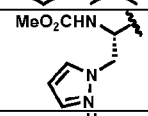
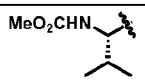
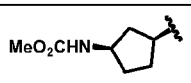
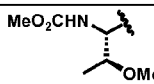
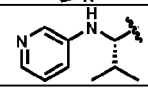
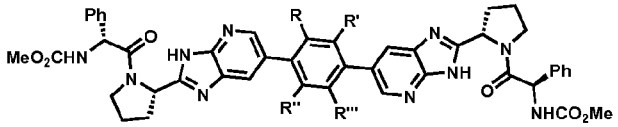
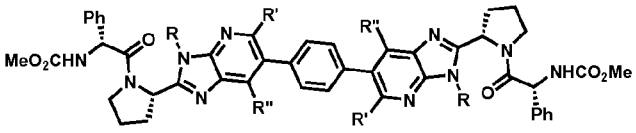
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 14: Compounds 2-264 to 2-273.



Entry 2-	R	R'	R"	R'"	Entry 2-	R	R'	R"	R'"
264	F	H	H	H	265	F	F	H	H
266	Me	H	H	H	267	Me	Me	H	H
268	H	H	Me	Me	269	H	H	Et	Et
270	CF_3	H	H	H	271	CF_3	H	CF_3	H
272	Cl	H	H	H	273	Cl	H	Cl	H

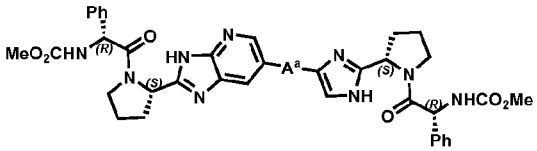
Table 15: Compounds 2-274 to 2-291.

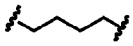
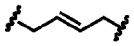
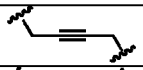
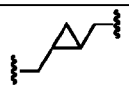
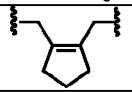
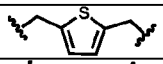
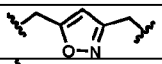
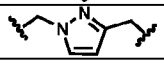
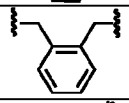
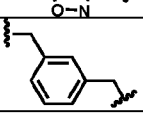
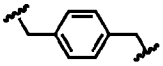
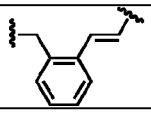
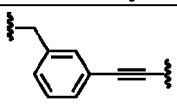
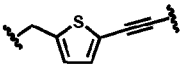
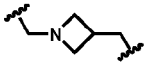
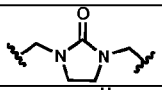
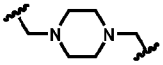
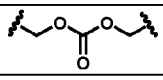
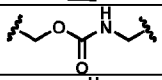
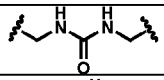
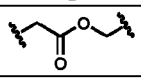
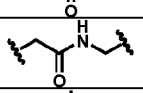
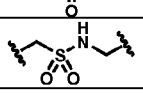
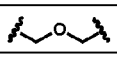
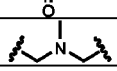
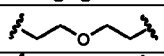
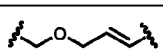
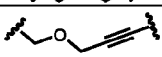
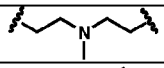
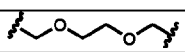
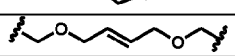
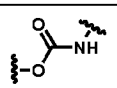
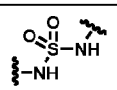
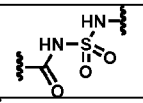
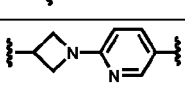
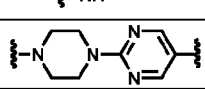
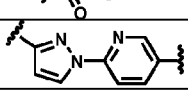


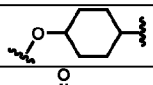
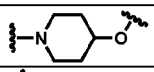
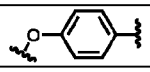
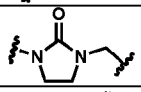
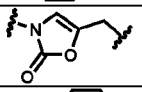
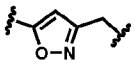
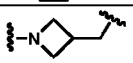
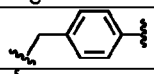
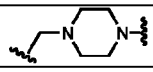
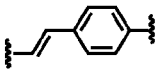
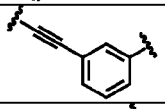
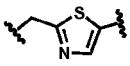
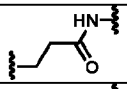
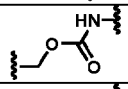
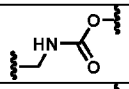
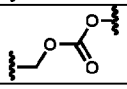
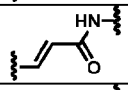
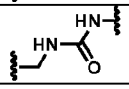
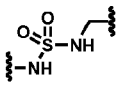
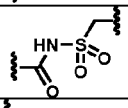
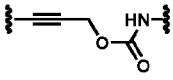
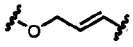
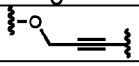
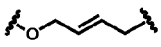
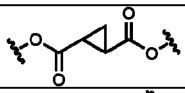
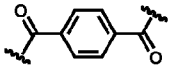
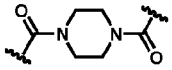
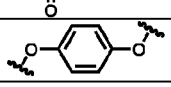
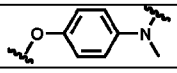
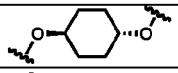
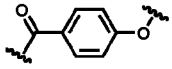
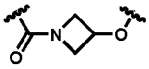
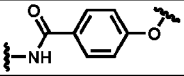
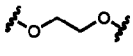
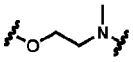
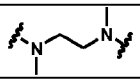
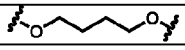
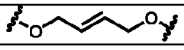
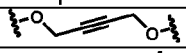
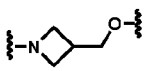
Entry 2-	R	R'	R"	Entry 2-	R	R'	R"
274	Me	H	H	275	H	CO_2H	H
276	H	F	H	277	H	H	CO_2H
278	H	H	F	279	H	CO_2Me	H

280	H	Cl	H	281	H	H	CO_2Me
282	H	H	Cl	283	H	$CONH_2$	H
284	H	Me	H	285	H	H	$CONH_2$
286	H	H	Me	287	H	OMe	H
288	H	CF_3	H	289	H	H	OMe
290	H	H	CF_3	291	CO_2Me	H	H

Table 16: Compounds 2-292 to 2-426.



Entry 2-	A^a	Entry 2-	A^a	Entry 2-	A^a
292		293		294	
295		296		297	
298		299		300	
301		302		303	
304		305		306	
307		308		309	
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	
337		338		339	

340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	
358		359		360	
361		362		363	
364		365		366	
367		368		369	
370		371		372	
373		374		375	
376		377		378	
379		380		381	
382		383		384	
385		386		387	
388		389		390	
391		392		393	
394		395		396	
397		398		399	

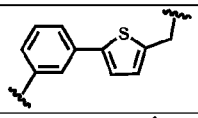
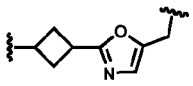
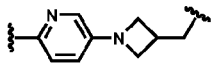
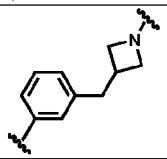
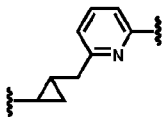
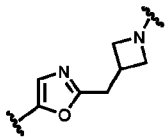
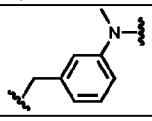
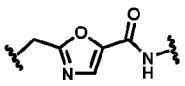
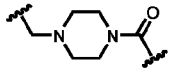
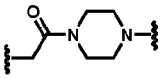
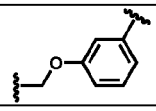
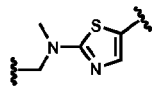
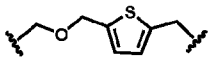
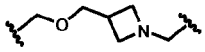
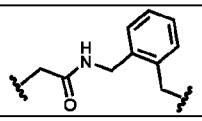
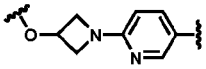
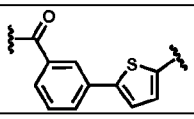
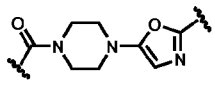
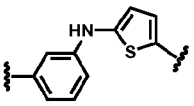
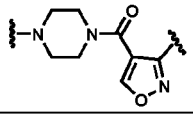
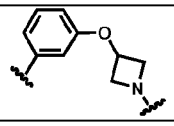
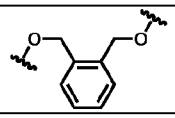
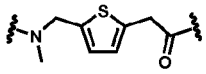
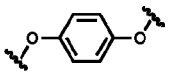
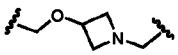
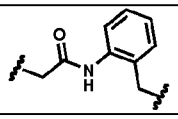
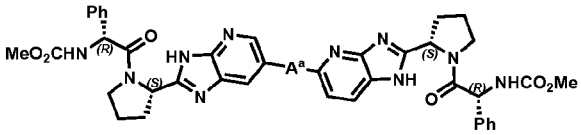
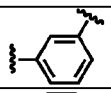
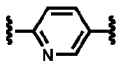
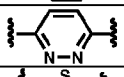
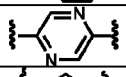
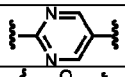
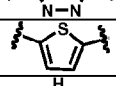
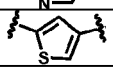
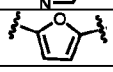
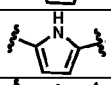
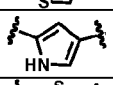
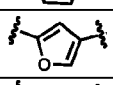
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409		410		411	
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415		416		417	
418		419		420	
421		422		423	
424		425		426	

Table 17: Compounds 2-427 to 2-477.



Entry 2-	A^a	Entry 2-	A^a	Entry 2-	A^a
427		428		429	
430		431		432	
433		434		435	
436		437		438	
439		440		441	
442		443		444	

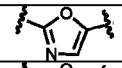
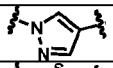
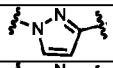
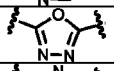
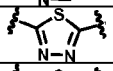
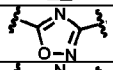
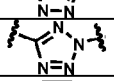
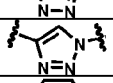
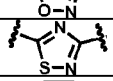
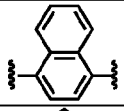
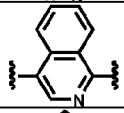
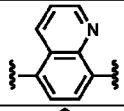
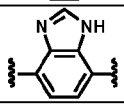
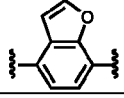
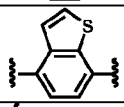
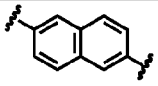
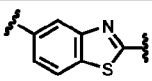
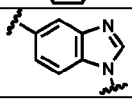
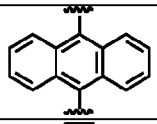
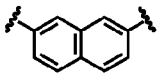
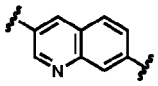
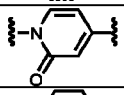
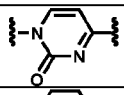
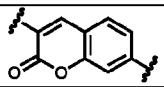
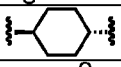
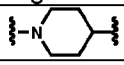
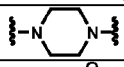
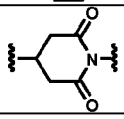
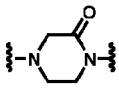
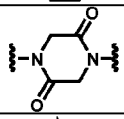
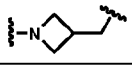
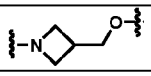
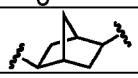
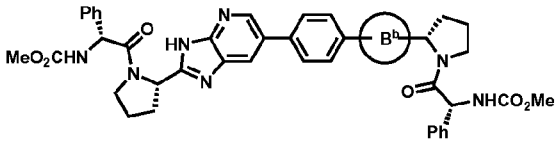
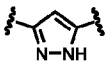
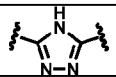
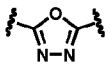
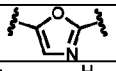
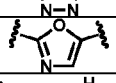
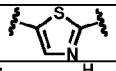
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448		449		450	
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454		455		456	
457		458		459	
460		461		462	
463		464		465	
466		467		468	
469		470		471	
472		473		474	
475		476		477	

Table 18: Compounds 2-478 to 2-497.



Entry 2-	B^b	Entry 2-	B^b	Entry 2-	B^b
478		479		480	
481		482		483	
484		485		486	
487		488		489	
490		491		492	
493		494		495	

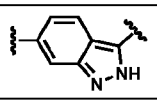
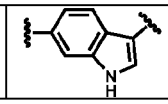
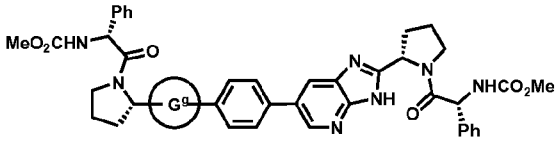
496		497			

Table 19: Compounds 2-498 to 2-508.



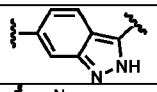
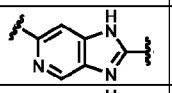
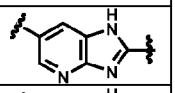
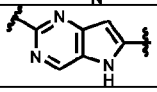
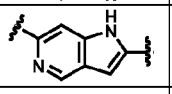
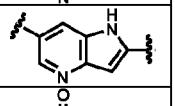
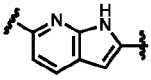
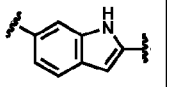
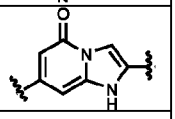
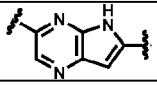
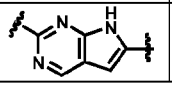
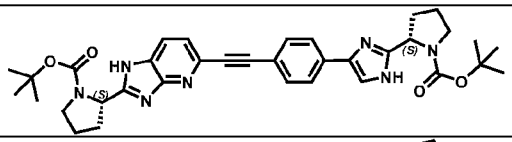
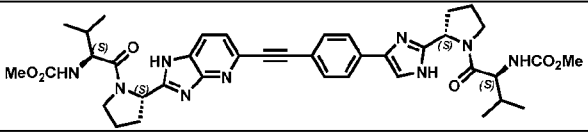
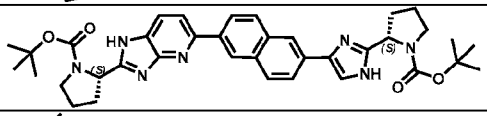
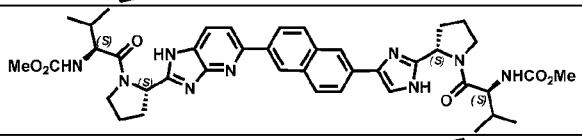
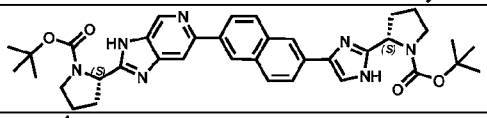
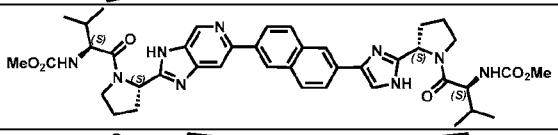
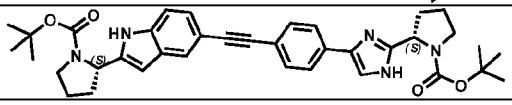
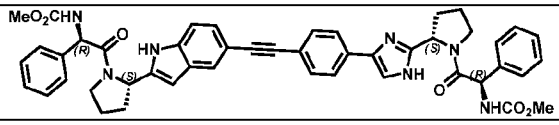
Entry 2-	G^g	Entry 2-	G^g	Entry 2-	G^g
498		499		500	
501		502		503	
504		505		506	
507		508			

Table 20: Compounds 2-509 to 2-516

2-509	
2-510	
2-511	
2-512	
2-513	
2-514	
2-515	

2-516	

It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substitutent at any given location.

It is intended that the definition of any substituent or variable (e.g., R^1, R^2, X, u, m, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

It will be yet appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. It will still be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

It should be understood that the compounds encompassed by the present invention are those that are suitably stable for use as pharmaceutical agent.

It will be further appreciated that reference herein to therapy and/or treatment includes, but is not limited to, prevention, retardation, prophylaxis, therapy and cure of the disease. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection includes treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

A further embodiment of the present invention includes pharmaceutical compositions comprising any single compound or a combination of two or more compounds delineated herein, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier or excipient.

Yet a further embodiment of the present invention is a pharmaceutical composition comprising any single compound or a combination of two or more compounds delineated herein, or a pharmaceutically acceptable salt thereof, in combination with one or more agents known in the art, with a pharmaceutically acceptable carrier or excipient.

It will be further appreciated that compounds of the present invention can be administered as the sole active pharmaceutical agent, or used in combination with one or more agents to treat or prevent hepatitis C infections or the symptoms associated with HCV infection. Other agents to be administered in combination with a compound or combination of compounds of the present invention include therapies for disease caused by HCV infection that suppresses HCV viral replication by direct or indirect mechanisms. These agents include, but are not limited to, host immune modulators (for example, interferon-alpha, pegylated interferon-alpha, consensus interferon, interferon-beta, interferon-gamma, CpG oligonucleo-tides and the like); antiviral compounds that inhibit host cellular functions such as inosine monophosphate dehydrogenase (for example, ribavirin and the like); cytokines that modulate immune function (for example, interleukin 2, interleukin 6, and interleukin 12); a compound that enhances the development of type 1 helper T cell response; interfering RNA; anti-sense RNA; vaccines comprising HCV antigens or antigen adjuvant combinations directed against HCV; agents that interact with host cellular components to block viral protein synthesis by inhibiting the internal ribosome entry site (IRES) initiated translation step of HCV viral replication or to block viral particle maturation and release with agents targeted toward the viroporin family of membrane proteins such as, for example, HCV P7 and the like; and any agent or combination of agents that inhibit the replication of HCV by targeting other proteins of the viral genome involved in the viral replication and/or interfere with the function of other viral targets, such as inhibitors of NS3/NS4A protease, NS3 helicase, NS5B polymerase, NS4A protein and NS5A protein.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise other inhibitor(s) of targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, NS4A protein, NS5A protein, and internal ribosome entry site (IRES).

Accordingly, one embodiment of the present invention is directed to a method for treating or preventing an infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents selected from the group consisting of a host immune modulator and a second or more antiviral agents, or a combination thereof, with a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. Examples of the host immune modulator

are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamrna, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

A further embodiment of the present invention is directed to a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver, with a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

Yet another embodiment of the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by hepatitis B (HBV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. An agent that treats patients for disease caused by hepatitis B (HBV) infection may be for example, but not limited thereto, L-deoxythymidine, adefovir, lamivudine or tenfovir, or any combination thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

Another further embodiment of the present invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt thereof. The agent that treats patients for disease caused by human immuno-deficiency virus (HIV) infection may include, but is not limited thereto, ritonavir, lopinavir, indinavir, nelfmavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir,

efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) or T-1249, or any combination thereof. A non-limiting example of the RNA-containing virus is hepatitis C virus (HCV).

It can occur that a patient may be co-infected with hepatitis C virus and one or more other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated herein is combination therapy to treat such co-infections by co-administering a compound according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

In addition, the present invention provides the use of a compound or a combination of compounds of the invention, or a therapeutically acceptable salt thereof, and one or more agents selected from the group consisting of a host immune modulator and one or more additional antiviral agents, or a combination thereof, to prepare a medicament for the treatment of an infection caused by an RNA-containing virus in a patient, particularly hepatitis C virus. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant. Preferably, said additional antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

When used in the above or other treatments, combination of compound or compounds of the present invention, together with one or more agents as defined herein above, can be employed in pure form or, where such forms exist, or as a pharmaceutically acceptable salt thereof. Alternatively, such combination of therapeutic agents can be administered as a pharmaceutical composition containing a therapeutically effective amount of the compound or combination of compounds of interest, or their pharmaceutically acceptable salt thereof, in combination with one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used for inhibiting the replication of an RNA-containing virus, particularly Hepatitis C virus (HCV), by contacting said virus with said pharmaceutical composition. In addition, such compositions are useful for the treatment or prevention of an infection caused by an RNA-containing virus, particularly Hepatitis C virus (HCV).

Hence, a still further embodiment of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus, particularly a hepatitis C virus (HCV), comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a compound or combination of compounds of the invention or a pharmaceutically acceptable salt thereof, and one or more agents as defined hereinabove, with a pharmaceutically acceptable carrier.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or within a predetermined period of time, or the therapeutic agents can be given as a single unit dosage form.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

Other agents that can be administered in combination with a compound of the present invention include a cytochrome P450 monooxygenase inhibitor (also referred to herein as a CYP inhibitor), which is expected to inhibit metabolism of the compounds of the invention. Therefore, the cytochrome P450 monooxygenase inhibitor would be in an amount effective to inhibit metabolism of the compounds of this invention. Accordingly, the CYP inhibitor is administered in an amount sufficient to improve one or more pharmacokinetic (PK) feautures including, but not limited to, plasma concentration, bioavailiablity, area under the plasma concentration time curve (AUC), elimination half-life, and systemic clearance, of a compound of the invention when one or more of its PK feautures of said compound is improved in comparison to that in the absence of the CYP inhibitor.

In one embodiment, the invention provides methods for improving the pharmaco-kinetics of compounds of the invention. The advantages of improving the pharmacokinetics of drugs are recognized in the art (see, for example, US Patent Pub. No.'s. 2004/0091527; US 2004/0152625; and US 2004/0091527). Accordingly, one embodiment of this invention provides a method comprising administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method comprising administering a compound of the invention

and an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In a preferred embodiment, the CYP inhibitor preferably inhibits CYP3A4. Any CYP inhibitor that improves the pharmacokinetics of the relevant compound of the invention may be used in a method of this invention. These CYP inhibitors include, but are not limited to, ritonavir (see, for example, WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, ditiazem, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention, is a pack comprising at least a compound of the invention and a CYP inhibitor and an information insert containing directions on the use of the combination of the invention. In an alternative embodiment of this invention, the pack further comprises one or more of additional agent as described herein. The additional agent or agents may be provided in the same pack or in separate packs.

Another aspect of this involves a packaged kit for a patient to use in the treatment of HCV infection or in the prevention of HCV infection, comprising: a single or a plurality of pharmaceutical formulation of each pharmaceutical component; a container housing the pharmaceutical formulation(s) during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat or prevent HCV infection.

Accordingly, this invention provides kits for the simultaneous or sequential administration of a compound of the invention and a CYP inhibitor (and optionally an additional agent) or derivatives thereof are prepared in a conventional manner. Typically, such a kit will comprise, e. g. a composition of a compound of the invention and optionally the additional agent (s) in a pharmaceutically acceptable

carrier (and in one or in a plurality of pharmaceutical formulations) and written instructions for the simultaneous or sequential administration.

In another embodiment, a packaged kit is provided that contains one or more dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package insert, a label, and/or on other components of the kit, and the dosage form or forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil- plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle. The present kits will also typically include means for packaging the individual kit components, i. e. , the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system comprising at least one aromatic ring, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, idenyl. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof.

The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof.

In accordance with the invention, aromatic groups can be substituted or unsubstituted.

The term "bicyclic aryl" or "bicyclic heteroaryl" refers to a ring system consisting of two rings wherein at least one ring is aromatic; and the two rings can be fused or covalently attached.

The terms "C_1-C_4 alkyl," "C_1-C_6 alkyl," "C_1-C_8 alkyl," "C_2-C_4 alkyl," or "C_3-C_6 alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and four, one and six, one and eight carbon atoms, or the like, respectively. Examples of C_1-C_8 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl and octyl radicals.

The terms "C_2-C_8 alkenyl," "C_2-C_4 alkenyl," "C_3-C_4 alkenyl," or "C_3-C_6 alkenyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight, or two to four carbon atoms, or the like, having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl, and the like.

The terms "C_2-C_8 alkynyl," "C_2-C_4 alkynyl," "C_3-C_4 alkynyl," or "C_3-C_6 alkynyl," as used herein, refer to straight- or branched-chain hydrocarbon radicals containing from two to eight, or two to four carbon atoms, or the like, having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl, and the like.

The term "C_3-C_8-cycloalkyl", or "C_5-C_7-cycloalkyl," as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring compound, and the carbon atoms may be optionally oxo-substituted. Examples of C_3-C_8-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C_5-C_7-cycloalkyl include, but not limited to, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and the like.

The term "C_3-C_8 cycloalkenyl" or "C_5-C_7 cycloalkenyl" as used herein, refers to monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond, and the carbon atoms may be optionally oxo-substituted. Examples of C_3-C_8 cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the

like; and examples of C_5-C_7 cycloalkenyl include, but not limited to, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like.

The term "arylalkyl", as used herein, refers to an aryl-substituted alkyl group. More preferred arylalkyl groups are aryl-C_1-C_6-alkyl groups.

The term "heteroarylalkyl", as used herein, refers to a heteroaryl-substituted alkyl group. More preferred heteroarylalkyl groups are heteroaryl-C_1-C_6-alkyl groups.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group or an alicyclic group.

An "aliphatic" group is a non-aromatic moiety comprised of any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contains one or more units of unsaturation, e.g., double and/or triple bonds. Examples of aliphatic groups are functional groups, such as, O, OH, NH, NH_2, C(O), $S(O)_2$, C(O)O, C(O)NH, OC(O)O, OC(O)NH, $OC(O)NH_2$, $S(O)_2NH$, $S(O)_2NH_2$, $NHC(O)NH_2$, NHC(O)C(O)NH, $NHS(O)_2NH$, $NHS(O)_2NH_2$, $C(O)NHS(O)_2$, $C(O)NHS(O)_2NH$ or $C(O)NHS(O)_2NH_2$, and the like, groups comprising one or more functional groups, non-aromatic hydrocarbons (optionally substituted), and groups wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a functional group. Carbon atoms of an aliphatic group can be optionally oxo-substituted. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, as used herein, aliphatic groups expressly include, for example, alkoxyalkyls, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Aliphatic groups may be optionally substituted. A linear aliphatic group is a non-cyclic aliphatic group. It is to be understood that when an aliphatic group or a linear aliphatic group is said to "contain" or "include" or "comprise" one or more specified functional groups, the linear aliphatic group can, for example, be selected from one or more of the specified functional groups or a combination thereof, or a group wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a specified functional group. In some examples, the aliphatic group can be represented by the formula M-Y-M', where M and M' are each independently absent or an alkyl, alkenyl or alkynyl, each optionally substituted, and Y is a

functional group. In some examples, Y is selected from the group consisting of $C(O)$, $S(O)_2$, $C(O)O$, $C(O)N(R^{11})$, $OC(O)O$, $OC(O)N(R^{11})$, $S(O)_2N(R^{11})$, $N(R^{11})C(O)N(R^{11})$, $N(R^{11})C(O)C(O)N(R^{11})$, $N(R^{11})S(O)_2N(R^{11})$, $C(O)N(R^{11})S(O)_2$ or $C(O)N(R^{11})S(O)_2N(R^{11})$; wherein R^{11} is as previously defined. In another aspect of the invention, an exemplary linear aliphatic group is an alkyl, alkenyl or alkynyl, each optionally substituted, which is interrupted or terminated by a functional group such as described herein.

The term "alicyclic," as used herein, denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom, and the carbon atoms may be optionally oxo-substituted. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The terms "heterocyclic" or "heterocycloalkyl" can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, 1,3-dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted. Heteroaryl or heterocyclic groups can be C-attached or N-attached (where possible).

It is understood that any alkyl, alkenyl, alkynyl, alicyclic, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclic, aliphatic moiety or the like, described herein can also be a divalent group when used as a linkage to connect two groups or substituents, which can be at the same or different atom(s).

The term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, $-NO_2$, $-N_3$, -CN, $-NH_2$, protected

amino, oxo, thioxo, -NH-C_1-C_{12}-alkyl, -NH-C_2-C_8-alkenyl, -NH-C_2-C_8-alkynyl, -NH-C_3-C_{12}-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_8-alkenyl, -O-C_2-C_8-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C_1-C_{12}-alkyl, -C(O)-C_2-C_8-alkenyl, -C(O)-C_2-C_8-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -$CONH_2$, -CONH-C_1-C_{12}-alkyl, -CONH-C_2-C_8-alkenyl, -CONH-C_2-C_8-alkynyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO_2-C_1-C_{12}-alkyl, -OCO_2-C_2-C_8-alkenyl, -OCO_2-C_2-C_8-alkynyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, -CO_2-C_1-C_{12} alkyl, -CO_2-C_2-C_8 alkenyl, -CO_2-C_2-C_8 alkynyl, CO_2-C_3-C_{12}-cycloalkyl, -CO_2- aryl, CO_2-heteroaryl, CO_2-heterocyloalkyl, -$OCONH_2$, -OCONH-C_1-C_{12}-alkyl, -OCONH-C_2-C_8-alkenyl, -OCONH-C_2-C_8-alkynyl, -OCONH-C_3-C_{12}-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocyclo-alkyl, -NHC(O)H, -NHC(O)-C_1-C_{12}-alkyl, -NHC(O)-C_2-C_8-alkenyl, -NHC(O)-C_2-C_8-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocyclo-alkyl, -$NHCO_2$-C_1-C_{12}-alkyl, -$NHCO_2$-C_2-C_8-alkenyl, -$NHCO_2$- C_2-C_8-alkynyl, -$NHCO_2$-C_3-C_{12}-cycloalkyl, -$NHCO_2$-aryl, -$NHCO_2$-heteroaryl, -$NHCO_2$- heterocycloalkyl, -$NHC(O)NH_2$, -NHC(O)NH-C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_8-alkenyl, -NHC(O)NH-C_2-C_8-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH-C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_8-alkenyl, -NHC(S)NH-C_2-C_8-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -$NHC(NH)NH_2$, -NHC(NH)NH-C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_8-alkenyl, -NHC(NH)NH-C_2-C_8-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_8-alkenyl, -NHC(NH)-C_2-C_8-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_8-alkenyl, -C(NH)NH-C_2-C_8-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, -S(O)-C_2-C_8-alkenyl, - S(O)-C_2-C_8-alkynyl, -S(O)-C_3-C_{12}-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, -SO_2NH_2, -SO_2NH-C_1-C_{12}-alkyl, -SO_2NH-C_2-C_8-alkenyl, -SO_2NH- C_2-C_8-alkynyl, -

SO_2NH-C_3-C_{12}-cycloalkyl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -SO_2NH-heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_8-alkenyl, - $NHSO_2$-C_2-C_8-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_8-alkenyl, -S-C_2-C_8-alkynyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthio-methyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

The term "halogen," as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

The term "hydrogen" includes hydrogen and deuterium. In addition, the recitation of an atom includes other isotopes of that atom so long as the resulting compound is pharmaceutically acceptable.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reaction. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert-butoxy-carbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl, benzyl, triphenyl-methyl (trityl), methoxymethyl, methylthiomethyl,

benzyloxymethyl, 2-(trimethylsilyl)-ethoxymethyl, methanesulfonyl, trimethylsilyl, triisopropylsilyl, and the like.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "hydroxy prodrug group", as used herein, refers to a promoiety group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group in vivo. Hydroxy prodrug groups as known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery, (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992).

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, methoxycarbonyl, t-butoxycarbonyl, 9-fluorenyl-methoxycarbonyl, benzyloxycarbonyl, and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride,

ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protic solvent' as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the Formula herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds.

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH (1999); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The term "subject" as used herein refers to an animal. Preferably, the animal is a mammal. More preferably, the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. Tautomers may be in cyclic or acyclic. The configuration of any carbon-carbon

double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis, trans*, or a mixture of the two in any proportion.

Certain compounds of the present invention may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of these compounds and mixtures thereof.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentane-propionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like.

Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of the invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, *et al.* (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, *J. of Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

The present invention also relates to solvates of the compounds of the invention, for example, hydrates.

This invention also encompasses pharmaceutical compositions containing, and methods of treating viral infections through administering, pharmaceutically acceptable prodrugs of compounds of the invention. For example, compounds of the invention having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating

material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminun hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert

diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at

body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.,* and WO 98/43650 by Montgomery, all of which are incorporated herein by reference). A discussion of pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

ANTIVIRAL ACTIVITY

An inhibitory amount or dose of the compounds of the present invention may range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections, conditions are treated or prevented in a patient such as a human or

another animal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment.

The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

The compounds of the present invention described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a

dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically exipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

When the compositions of this invention comprise a combination of a compound of the Formula described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be

part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The said "additional therapeutic or prophylactic agents" includes but not limited to, immune therapies (eg. interferon), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (eg ribavirin and amantidine). The compositions according to the invention may also be used in combination with gene replacement therapy.

COMBINATION AND ALTERNATION THERAPY FOR HCV

It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for a protein such as an enzyme used in viral replication, and most typically in the case of HCV, RNA polymerase, protease, or helicase.

Recently, it has been demonstrated that the efficacy of a drug against a viral infection, such as HIV, can be prolonged, augmented, or restored by administering the drug in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principal drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

A compound of the present invention can also be administered in combination or alternation with antiviral agent. Examplary antiviral agents include ribavarin, interferon, interleukin or a stabilized prodrug of any of them. More broadly described, the compound can be administered in combination or alternation with any of the anti-HCV drugs listed in Table 21 below.

Table 21

Table of anti-Hepatitis C Compounds in Current Clinical Development		
Drug name	Drug category	Pharmaceutical Company
PEGASYS pegylated interferon alfa-2a	Long acting interferon	Roche
INFERGEN interferon alfacon-1	Long acting interferon	InterMune
OMNIFERON natural interferon	Long acting interferon	Viragen
ALBUFERON	Long acting interferon	Human Genome Sciences
REBIF interferon beta-la	Interferon	Ares-Serono
Omega Interferon	Interferon	BioMedicine
Oral Interferon alpha	Oral Interferon	Amarillo Biosciences
Interferon gamma-lb	Anti-fibrotic	InterMune
IP-501	Anti-fibrotic	InterMune
Merimebodib VX-497	IMPDH inhibitor (inosine monophosphate dehydrogenase)	Vertex
AMANTADINE (Symmetrel)	Broad Antiviral Agent	Endo Labs Solvay
IDN-6556	Apotosis regulation	Idun Pharma.
XTL-002	Monclonal Antibody	XTL
HCV/MF59	Vaccine	Chiron
CIVACIR	Polyclonal Antibody Therapeutic vaccine	NABI Innogenetics
VIRAMIDINE	Nucleoside Analogue	ICN
ZADAXIN (thymosin alfa-1)	Immunomodulator	Sci Clone
CEPLENE (histamine)	Immunomodulator	Maxim
VX 950/LY 570310	Protease inhibitor	Vertex/Eli Lilly
ISIS 14803	Antisense	Isis Pharmaceutical/Elan
IDN-6556	Caspase inhibitor	Idun Pharmaceuticals
JTK 003	Polymerase Inhibitor	AKROS Pharma
Tarvacin	Anti-Phospholipid Therapy	Peregrine
HCV-796	Polymerase Inhibitor	ViroPharma/Wyeth
CH-6	Protease inhibitor	Schering
ANA971	Isatoribine	ANADYS
ANA245	Isatoribine	ANADYS
CPG 10101 (Actilon)	Immunomodulator	Coley
Rituximab (Rituxam)	Anti-CD2O Monoclonal Antibody	Genetech/IDEC
NM283 (Valopicitabine)	Polymerase Inhibitor	Idenix Pharmaceuticals
HepX™-C	Monoclonal Antibody	XTL
IC41	Therapeutic Vaccine	Intercell
Medusa Interferon	Longer acting interferon	Flamel Technology
E-1	Therapeutic Vaccine	Innogenetics
Multiferon	Long Acting Interferon	Viragen
BILN 2061	Protease inhibitor	Boehringer-Ingelheim
TMC435350	Protease inhibitor	Tibotec/Medivir
Telaprevir (VX-950)	Protease inhibitor	Vertex
Boceprevir (SCH 503034)	Protease inhibitor	Schering-Plough
ACH-1625	Protease inhibitor	Achillion
ABT-450	Protease inhibitor	Abbott/Enanta
BI-201335	Protease inhibitor	Boehringer-Ingelheim
PHX-1766	Protease inhibitor	Phenomix

VX-500	Protease inhibitor	Vertex
MK-7009	protease inhibitor	Merck
R7227 (ITMN-191)	protease inhibitor	InterMune
Narlaprevir (SCH 900518)	Protease inhibitor	Schering/Merck
Alinia (nitazoxanide)	To be determined	Romark
ABT-072	Polymerase Inhibitor	Abbott
ABT-333	Polymerase Inhibitor	Abbott
Filibuvir (PF-00868554)	Polymerase Inhibitor	Pfizer
VCH-916	Polymerase Inhibitor	Vertex
R7128 (PSI6130)	Polymerase Inhibitor	Roche/Pharmasset
IDX184	Polymerase Inhibitor	Idenix
R1626	Polymerase inhibitor	Roche
MK-3281	Polymerase inhibitor	Merck
PSI-7851	Polymerase inhibitor	Pharmasset
ANA598	Polymerase inhibitor	Anadys Pharmaceuticals
BI-207127	Polymerase inhibitor	Boehringer-Ingelheim
GS-9190	Polymerase inhibitor	Gilead
VCH-759	Polymerase Inhibitor	Vertex
Clemizole	NS4B inhibitor	Eiger Biopharmaceuticals
A-832	NS5A inhibitor	ArrowTherapeutics
BMS-790052	NS5A inhibitor	Bristol-Myers-Squibb
ITX5061	Entry inhibitor	iTherx
GS-9450	Caspase inhibitor	Gilead
ANA773	TLR agonist	Anadys
CYT107	immunomodulator	Cytheris
SPC3649 (LNA-antimiR™-122)	microRNA	Santaris Pharma
Debio 025	Cyclophilin inhibitor	Debiopharm
SCY-635	Cyclophilin inhibitor	Scynexis

Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one of ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

ABBREVIATIONS

Abbreviations which may be used in the descriptions of the scheme and the examples that follow are: Ac for acetyl; AcOH for acetic acid; AIBN for azobisisobutyronitrile; BINAP for 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc_2O for di-*tert*-butyl-dicarbonate; Boc for *t*-butoxycarbonyl; Bpoc for 1-methyl-1-(4-biphenylyl)ethyl carbonyl; BtOH for 1-hydroxy-benzotriazole; Bz for benzoyl; Bn for benzyl; BocNHOH for *tert*-butyl N-hydroxycarbamate; t-BuOK for potassium *tert*-butoxide; Bu_3SnH for tributyltin hydride; BOP for (benzotriazol-1-yloxy)tris(dimethylamino)phos-phonium Hexafluorophosphate; Brine for sodium chloride solution in water; Cbz for carbobenzyloxy; CDI for carbonyldiimidazole; CH_2Cl_2 for dichloromethane; CH_3 for methyl; CH_3CN for acetonitrile; Cs_2CO_3 for

cesium carbonate; CuCl for copper (I) chloride; CuI for copper (I) iodide; dba for dibenzylidene acetone; dppb for diphenylphosphino butane; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC for N,N'-dicyclohexylcarbodiimide; DEAD for diethylazodicarboxylate; DIAD for diisopropyl azodicarboxylate; DIBAL-H for diisobutylaluminium hydride; DIPEA or $(i\text{-}Pr)_2EtN$ for N,N-diisopropylethyl amine; Dess-Martin periodinane for 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one; DMAP for 4-dimethylaminopyridine; DME for 1,2-dimethoxy-ethane; DMF for N,N-dimethylformamide; DMSO for dimethyl sulfoxide; DMT for di(*p*-methoxyphenyl)phenylmethyl or dimethoxytrityl; DPPA for diphenylphosphoryl azide; EDC for N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide; EDC HCl for N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide hydrochloride; EtOAc for ethyl acetate; EtOH for ethanol; Et_2O for diethyl ether; Fmoc for 9-fluorenylmethoxycarbonyl; Grubbs-1 catalyst for benzylidene-bis(tricyclohexylphosphine)dichlororuthenium; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HCl for hydrogen chloride; HOBT for 1-hydroxybenzotriazole; K_2CO_3 for potassium carbonate; *n*-BuLi for *n*-butyl lithium; *i*-BuLi for *i*-butyl lithium; *t*-BuLi for *t*-butyl lithium; PhLi for phenyl lithium; LDA for lithium diisopropylamide; LiTMP for lithium 2,2,6,6-tetramethylpiperidinate; MeOH for methanol; Mg for magnesium; MOM for methoxymethyl; Ms for mesyl or $-SO_2-CH_3$; Ms_2O for methanesulfonic anhydride or mesyl-anhydride; $NaBH_4$ for sodium borohydride; $NaBH_3CN$ for sodium cyanoborohydride; NaN(TMS)2 for sodium bis(trimethylsilyl)amide; NaCl for sodium chloride; NaH for sodium hydride; $NaHCO_3$ for sodium bicarbonate or sodium hydrogen carbonate; Na_2CO_3 sodium carbonate; NaOH for sodium hydroxide; Na_2SO_4 for sodium sulfate; $NaHSO_3$ for sodium bisulfite or sodium hydrogen sulfite; $Na_2S_2O_3$ for sodium thiosulfate; NH_2NH_2 for hydrazine; NH_4HCO_3 for ammonium bicarbonate; NH_4Cl for ammonium chloride; NMMO for N-methylmorpholine N-oxide; $NaIO_4$ for sodium periodate; Ni for nickel; OH for hydroxyl; OsO_4 for osmium tetroxide; Pd for palladium; Ph for phenyl; PMB for p-methoxybenzyl; POPd for dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(II); $Pd_2(dba)_3$ for tris(dibenzylidene-acetone) dipalladium (0); $Pd(PPh_3)_4$ for tetrakis(triphenylphosphine)palladium (0); $PdCl_2(PPh_3)_2$ for trans-dichlorobis(triphenyl-phosphine)palladium (II); Pt for platinum; Rh for rhodium; rt

for romm temperature; Ru for ruthenium; SEM for (trimethylsilyl)ethoxymethyl; TBAF for tetrabutylammonium fluoride; TBS for *tert*-butyl dimethylsilyl; TEA or Et_3N for triethylamine; Teoc for 2-trimethylsilyl-ethoxy-carbonyl; TFA for trifluoroacetic acid; THF for tetrahydrofuran; TMEDA for N,N,N',N'-tetramethylethylenediamine; TPP or PPh_3 for triphenyl-phosphine; Troc for 2,2,2-trichloroethyl carbonyl; Ts for tosyl or $-SO_2-C_6H_4CH_3$; Ts_2O for tolylsulfonic anhydride or tosyl-anhydride; TsOH for p-tolylsulfonic acid; TMS for trimethylsilyl; or TMSCl for trimethylsilyl chloride.

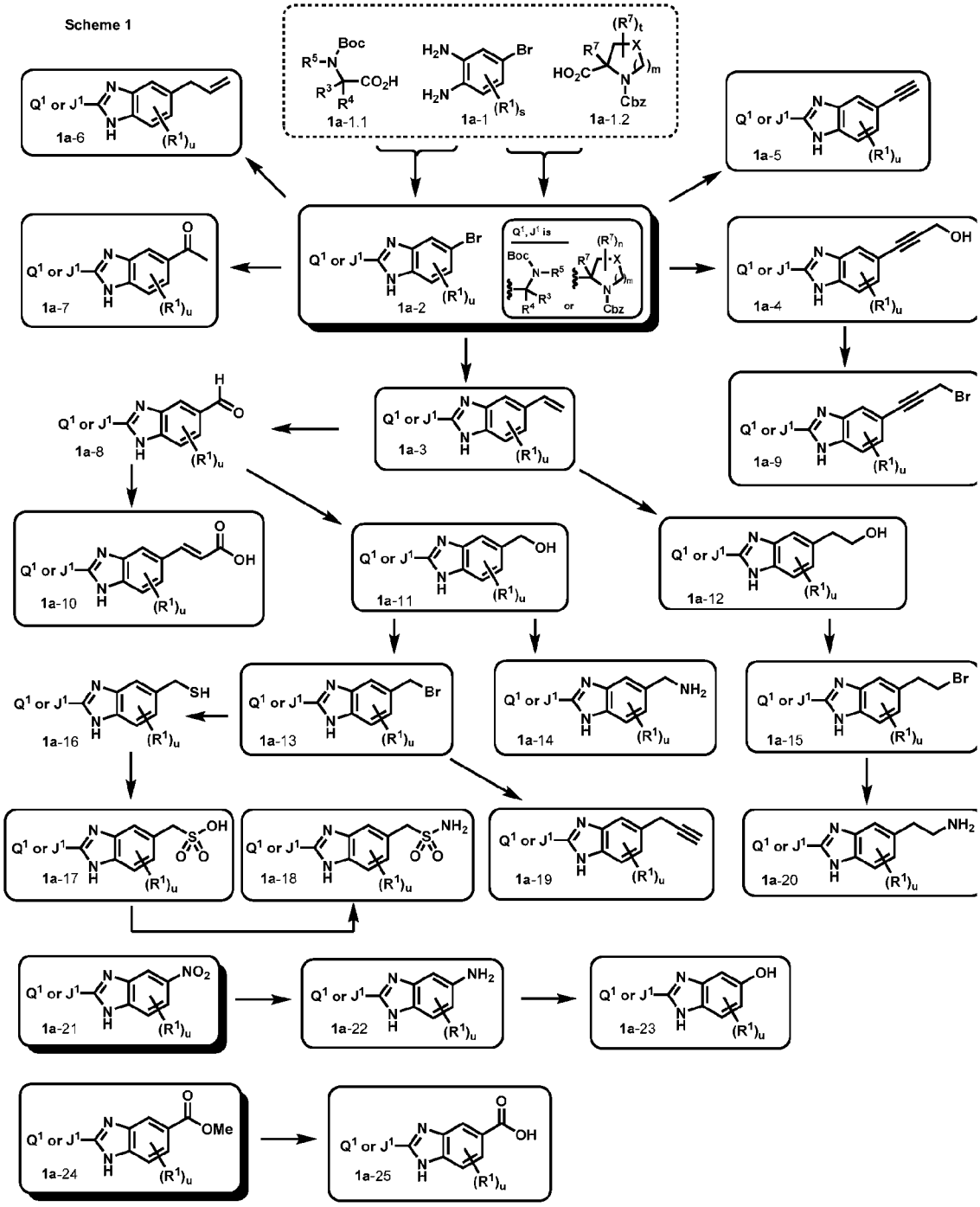
SYNTHETIC METHODS

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

The compounds of the present invention may be prepared via several different synthetic routes from a variety of 5/6-membered fused heteroaryl, 5-membered heteroaryl, and related intermediates. A retro-synthesis of those title compounds include direct formation of a suitably linked 5/6-membered fused heteroaryl with a 5/6-membered fused heteroaryl or 5-membered heteroaryl core structure followed by attachment of a suitable R^6 group, plus some functional group manipulations in between and/or after. Various 5/6-membered fused heteroaryl or 5-membered heteroaryl intermediates are known to those skilled in the art, for example see the encyclopedic volumns edited by A. R. Katrizky, et al, "Comprehensive Heterocyclic Chemistry" 1984; "Comprehensive Heterocyclic Chemistry II" 1996; "Comprehensive Heterocyclic Chemistry III" 2008.

A general synthesis and further elaboration of some benzimidazole related intermediates are summarized in Scheme 1.

The synthesis starts from the construction of an optionally substituted benzimidazole **1a**-2, which may be obtained by condensation of an amino acid or its derivative **1a**-1.1 or **1a**-1.2 and an *o*-phenylenediamine **1a**-1 under the conditions to those skilled in the art. The benzimidazole ring closure may be realized either in one pot by heat, optionally in the presence of an acid and/or with a dehydration reagent such as polyphosphoric acid; or in two steps: 1) amide formation between diamine **1a**-1 and amino acid **1a**-1.1 or **1a**-1.2 in the presence of a condensation reagent such as EDC HCl, DCC or the like; or through mixed anhydride approach by reacting acid **1a**-1.1 or **1a**-1.2 with a chloroformate such as methyl chloroformate, isobutyl chloroformate, or the like, in the presence of a base such as TEA, DIPEA, DMAP, N-methylmorpholine, or the like, followed by treating the mixed anhydride with diamine **1a**-1; and 2) the heterocyclic ring closure in the presence of an acid such as acetic acid, sulfuric acid or the like or a dehydration reagent such as HATU or the like, optionally with heat.



Optionally, the NH group in the newly formed benzimidazole ring of **1a**-2 may be protected with an amino protecting group, such as SEM (i.e. SEM-Cl, NaH), Boc, Cbz, Teoc, Troc, or the like. The protected benzimidazole **1a**-2 may be subjected to lithium-halogen exchange with various (*n*-, *s*-, or *t*-) butyl lithium and the resulting lithiate can be trapped with a nucleophile, i.e. a halide such as various allyl halide to give the allylated **1a**-6 as a key intermediate. Alternatively, **1a**-6 may

be obtained from the Stille reaction conditions to those skilled in the art (see reviews: A. Anastasia, et al, *Handbook of Organopalladium Chemistry for Organic Synthesis* 2002, 1, 311; F. Bellina, et al, *Synthesis* 2004, 2419; M. G. Organ, et al, *Synthesis* 2008, 2776; A. T. Lindhardt, et al, *Chem. - A European J.* 2008, 14, 8756; E. A. B. Kantchev, et al, *Angew. Chem. Int. Ed.* 2007, 46, 2768; V. Farina, et al, *Advances in Metal-Organic Chem.* 1996, 5, 1), using an allylstanne such as allyltributylstanne as the allyl donor. Analogously a key vinyl intermediates **1a**-3 may be prepared by Stille reaction from bromide **1a**-2 with tributylvinylstanne. Also, Sonogashira coupling between bromide **1a**-2 and propargyl alcohol or trimethylsilylacetylene can generate propargyl alcohol **1a**-4 or alkyne **1a**-5 after removal of TMS. Further bromination of intermediate **1a**-4 may form the propargyl bromide **1a**-9. In addition, benzimidazole bromide **1a**-2 may be converted to methyl ketone **1a**-7 by coupling with tributyl(1-ethoxyvinyl)tin under Stille coupling conditions followed by acidic hydrolysis.

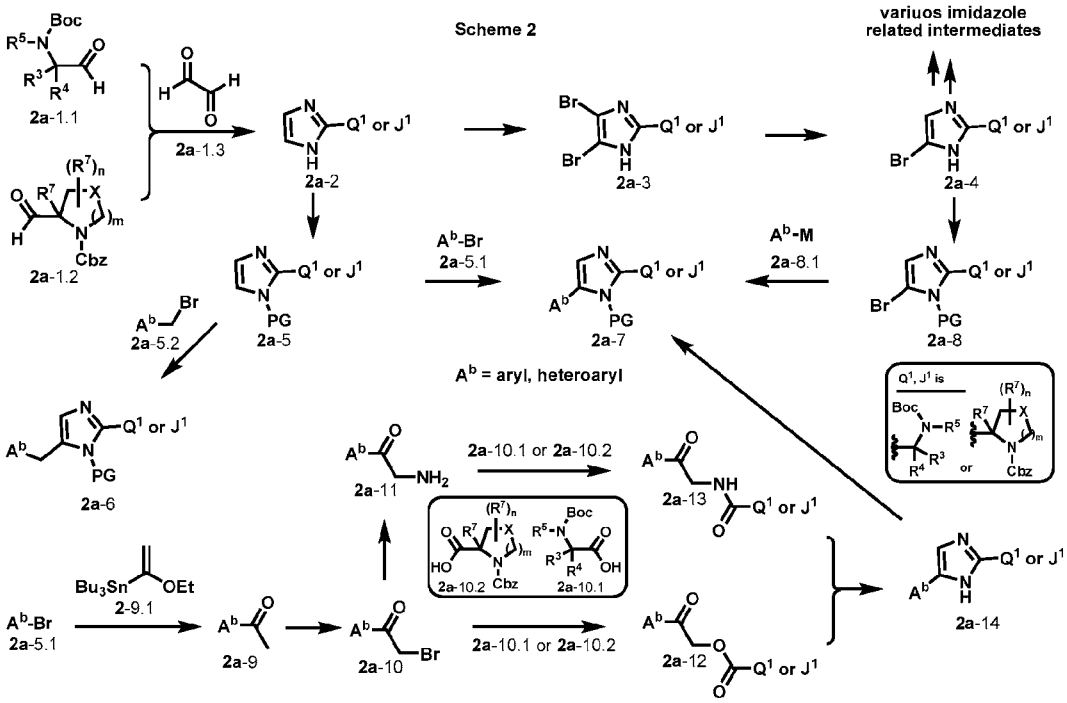
Further elaboration of the benzimidazole intermediates starts from the vinyl intermediate **1a**-3, which may be transformed to aldehyde **1a**-8 through ozonolysis cleavage or to alcohol **1a**-12 by hydroboration-oxidation sequence. Alcohol **1a**-12 may be converted to bromide **1a**-15 by the well-known bromination procedure, which can be further functionalized to amine **1a**-20 through azide substitution followed by reduction. Aldehyde **1a**-8 can then either be reduced to alcohol **1a**-11, or be converted to α, β-unsatuated acid **1a**-10 through Horner-Wadsworth-Emmons aldehyde homologation reaction followed by saponification. Alcohol **1a**-11 may be similarly converted to the correponding amine intermediate **1a**-14 and bromide intermediate **1a**-13 as described previously. Bromide **1a**-13 can be homologated to alkyne intermediate **1a**-19 with a metal acetylide. In addition, bromide **1a**-13 may be also tranformed to thiol **1a**-16 through nucleophilic substitution, which can be further oxidized to sulfonic acid **1a**-17. Sulfonamide **1a**-18 may then be derived from **1a**-17 through the sulfonyl chloride activation process.

The compounds of the present invention may also be derived from nitrobenzimidazole **1a**-21, which can be prepared from the corresponding 4-nitro-1,2-diaminobenzene using the similar procedures described above. Intermediate **1a**-21 can be converted to amine **1a**-22 through NO_2-reduction (i.e. H_2, catalytical Pd). Diazotization of amine **1a**-22 with a nitrite such as sodium nitrite, isobutyl nitrite, or the like, in an aqueous acid such as acetic acid, hydrochloric aicd, sulfuric acid, or

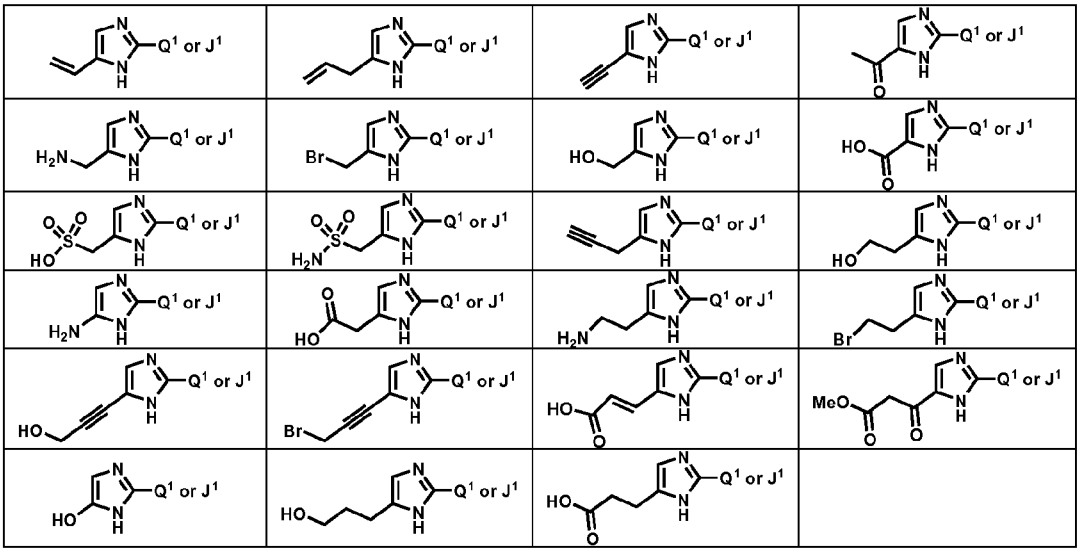
the like, optionally in the presence of a copper or copper salt, may afford hydroxy **1a**-23.

Analogously, benzimidazolecarboxylate **1a**-24, which can be prepared from the corresponding 4-methyl-1,2-diaminobenzoate using the procedures described above, may be hydrolyzed to the corresponding carboxylic acid **1a**-25.

It should be noted that optionally the NH group of all the benzimidazole related intermediates listed above may be protected with an amino protecting group, such as SEM (i.e. SEM-Cl, NaH), Boc, Cbz, Teoc, Troc, or the like.



A typical synthesis of imidazole related intermedaites are analogous to that of the benzimidazole intermediates. As shown in Scheme 2, bromo-imidazole **2a**-4 can be synthesized in a three-step sequence: 1) condensation between amino acid derived aldehyde **2a**-1.1 or **2a**-1.2 and glyoxal **2a**-1.3 in the presence of methanolic ammonia to generate imidazole **2a**-2; 2) bromination of **2a**-2 with excess amount of bromination reagent such as 2,4,4,6-tetrabromo-2,5-cyclohexadienone, NBS, etc. to afford dibromide **2a**-3; 3) selective reduction of the dibromide **2a**-3 by heating in aq. Na_2SO_3 or aq. $NaHSO_3$. **2a**-4 then may be served as a universal intermediate further elaborable to many other imidazole derivatives using the chemistry discussed in Scheme 1, some of which are listed in the table below.



Optionally, the NH group of imidazole related intermediates listed above may be protected with an amino protecting group (shown in Scheme 2 as PG), such as SEM (i.e. SEM-Cl, NaH), Boc, Cbz, Teoc, Troc, or the like. The protected imidazole **2a**-5 may be deprotonated with a strong base such as LDA, BuLi, etc to generate a carbon anion, which may either undergo a nucleophilic substitution with an activated halide such as **2a**-5.2 to afford aryl or heteroaryl substituted imidazole **2a**-6 or couple with an aryl or heteroaryl halide **2a**-5.1 in the presence appropriate transition metal salt to generate bicyclic heteroaryl **2a**-7. Similarly, the protected bromo imidazole **2a**-8 may be subjected to lithium-halogen exchange with various (*n*-, *s*-, or *t*-) butyl lithium, the resulting lithiate may undergo similar reactions to afford **2a**-6 and **2a**-7. Also, when **2a**-8 is treated with metalated aryl or heteroaryl **2a**-8.1, in which M at each occurrence is independently a boron, tin, silicon, zinc, zirconium, or copper species, under Suzuki or Stille conditions to those skilled in the art (see reviews: A. Suzuki, *Pure Applied Chem.* 1991, 63, 419; A. Suzuki, *Handbook of Organopalladium Chemistry for Organic Synthesis* 2002, 1, 249; A. Anastasia, et al, *Handbook of Organopalladium Chemistry for Organic Synthesis* 2002, 1, 311; F. Bellina, et al, *Synthesis* 2004, 2419; M. G. Organ, et al, *Synthesis* 2008, 2776; A. T. Lindhardt, et al, *Chem. - A European J.* 2008, 14, 8756; E. A. B. Kantchev, et al, *Angew. Chem. Int. Ed.* 2007, 46, 2768; V. Farina, et al, *Advances in Metal-Organic Chem.* 1996, 5, 1), to provide coupling product **2a**-7. In addition to these direct coupling strategy, aryl or heteroaryl bromide **2a**-5.1 may be converted to methyl ketone **2a**-9 under Stille coupling conditions with tributyl(1-ethoxyvinyl)tin

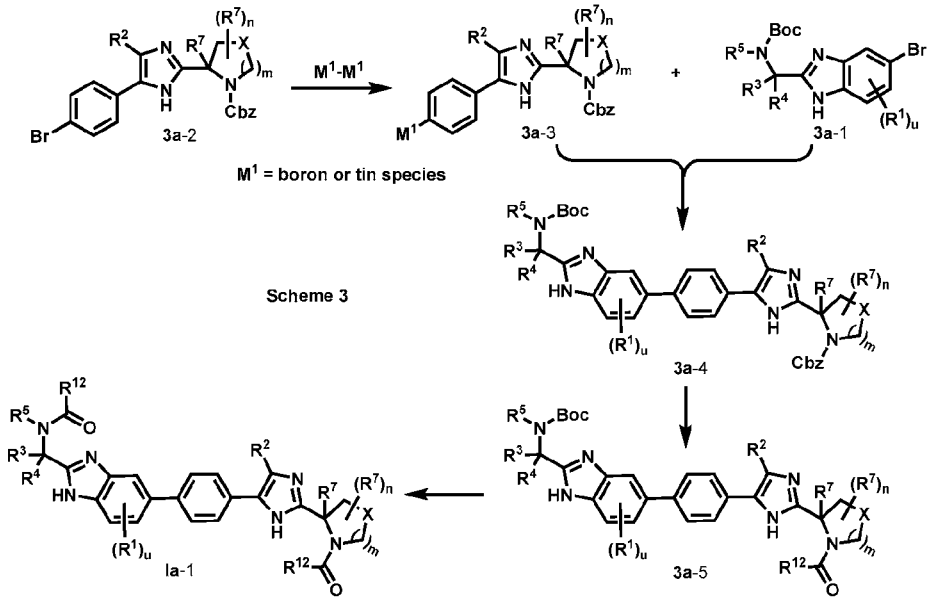
2a-9.1. **2a**-9 may be brominated under conditions to those skilled in the art to afford bromide **2a**-10, which may be either converted to the corresponding amine **2a**-11, or coupled with protected amino acid **2a**-10.1 or **2a**-10.2 in the presence of a base such as Et_3N and DIPEA to afford ketoester **2a**-12. Similarly, amine **2a**-11 may be converted to the corresponding keto-amide **2a**-13 via condensation with appropriate amino acid under standard amide formation conditions. **2a**-12 and **2a**-13 may be tranformed to key intermediate **2a**-14 via heating with $(NH_4)OAc$ under thermal or microwave conditions.

With a variety of suitably substituted benzimidazoles and imidazoles in hand, such as those listed in Scheme 1, Scheme 2 and the table above, the compounds of the present invention may be prepared through various coupling strategy or a combination of strategies to connect two fragments, optionally with a suitable cyclic or acyclic linker or formation of a cyclic or acyclic linker. The said strategy includes, but not limited to, Stille coupling, Suzuki coupling, Sonogashira coupling, Heck coupling, Buchwald amidation, Buchwald amination, amide coupling, ester bond formation, William etherification, Buchwald etherification, alkylation, pericyclic reaction with different variations, or the like.

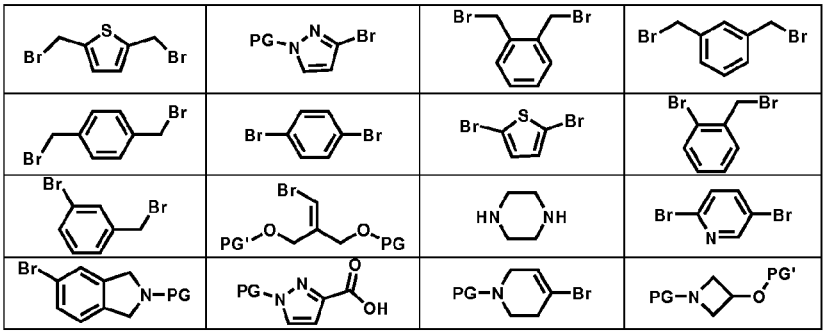
An example of the strategies that may be used to prepare the compounds of the present invention is shown in Scheme 3, wherein R^2 is independently R^1. Both bromides **3a**-1 and **3a**-2 can be prepared using the procedures described in Scheme 1 and Scheme 2. Bromide **3a**-2 can be converted to the corresponding metalated aryl **3a**-3 under Suzuki or Stille conditions, which may be further coupled with benzimidazole bromide **2a**-1 under similar conditions to generate a structural core **3a**-4.

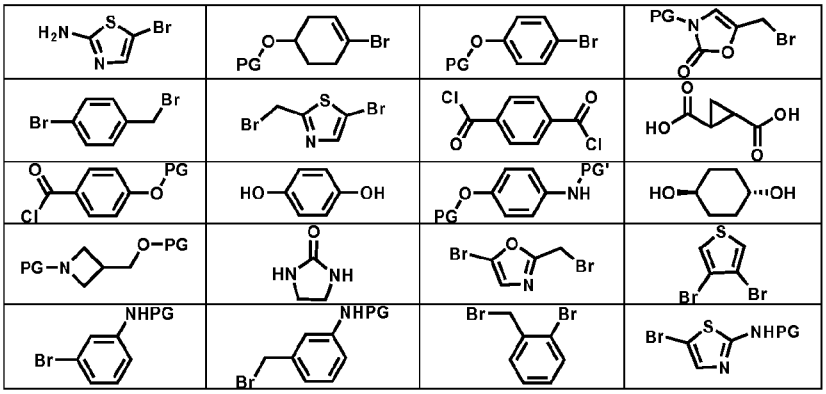
Compound **3a**-4 may then serve as a common intermediate for further derivatizations to **3a**-5 in two steps: 1) mono-deprotection of the linear or cyclic amine moiety may be accomplished, for example, treatment to hydrogenolytic conditions under Pd catalyst in the presence of a base such as potassium carbonate to remove the Cbz protection group; and 2) the released amine functionality may be acylated with an carboxylic acid under standard acylation conditions, for example a coupling reagent such as HATU in combination with an organic base such as DIPEA can be used in this regard; alternatively, the released amine may be reacted with an isocyanate, carbamoyl chloride or chloroformate to provide an urea or carbamate. Various carboxylic acids including amino acids in racemic or optical form are

commercially available, and/or can be synthesized in racemic or optical form, see references cited in reviews by D. Seebach, et al, *Synthesis* 2009, 1; C. Cativiela and M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* 2007, 18, 569; 2000, 11, 645; and 1998, 9, 3517; and experimental examples compiled in patent application WO 2008/021927A2 by C. Bachand, et al, from BMS, which is incorporated herein by reference. **3a**-5 may be further deprotected under hydrolytic conditions in the presence of an acid such as TFA or hydrogen chloride to remove the Boc protection group and the released amine functionality can be further derivatized to the title compounds **Ia**-1 using the conditions described above.

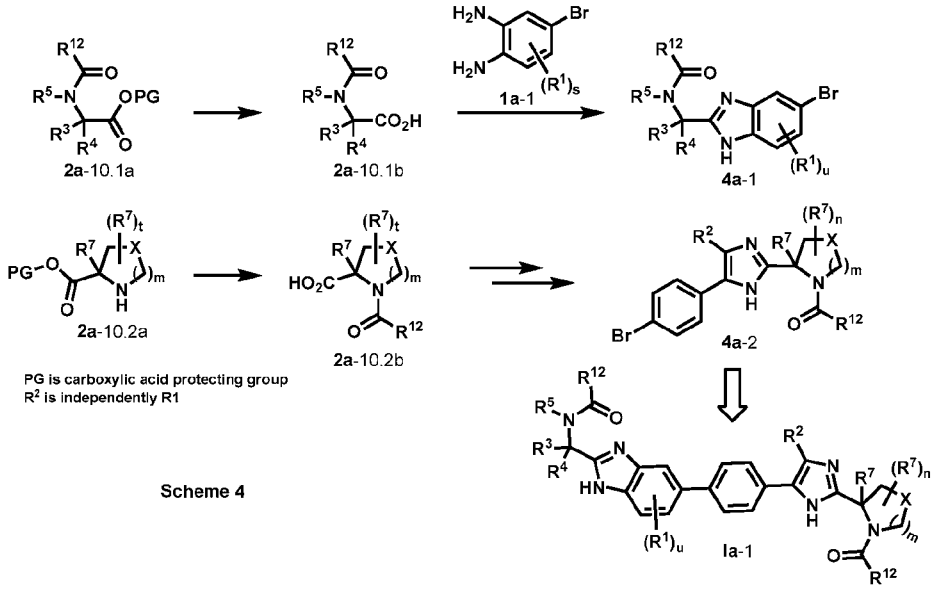


Other examples of some of the linkers that can be used to construct the title compounds of the present invention are compiled in the table below, in which PG and PG' at each occurrence are each independently amino or alcohol protecting group, such as Boc, Cbz, Troc, Teoc, PMB, TMS etc. These linkers are either commercially available or may be synthesized in several steps through strategies which are known to those skilled in the art.



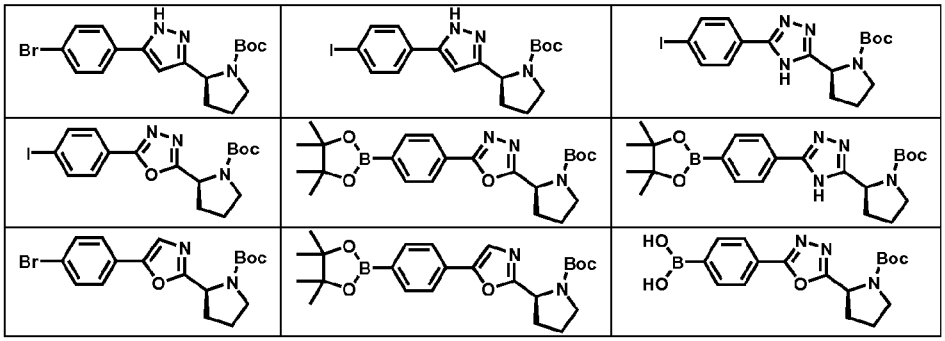


Alternatively, as shown in Scheme 4, the compounds of the present invention (for example **Ia**-1) may also be derived from bromobenzimidazoles **4a**-1 and imidazole **4a**-2 using the procedures described previously. The intermediates **4a**-1 and **4a**-2 have the desired acyl groups already installed as seen in amino acid derivatives **2a**-10.1b and **2a**-10.2b, which can be prepared from protected amino acids **2a**-10.1a and **2a**-10.2a through the sequences shown in Scheme 1 and 2.

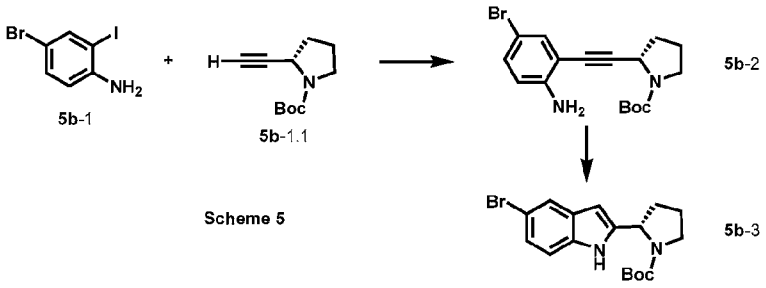


Scheme 4

The compounds of the present invention containing benzimidazole linked with other five-membered heteroaryl other than imidazole may be prepared using similar procedures described above in Schemes 1-4. For example, some intermediates containing a desired, suitably substituted five-membered heteroaryl have been published in US 2008/0311075A1 by C. Bachand, et al from BMS, which is incorporated by reference. Theses intermediates are compiled in the following table.



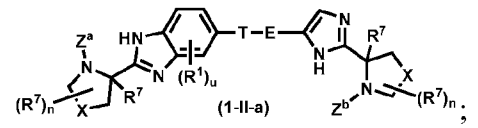
The synthesis of the compounds of the present invention involves 5/6-membered fused heteroaryl intermediates other than benzimidazoles, various 5/6-membered fused heteroaryl are known in the literature. For example, it may be possible to prepare various 3H-imidazo[4,5-b]pyridine intermediates following similar procedures described in Scheme 1 by replacing 4-bromo-1,2-diaminobenzene **1a**-1 with 5-bromo-2,3-diaminopyridine as starting material. The synthesis of other 5/6-membered fused heteroaryl intermediates depends on the chemical features of each structure. For example, a typical synthesis of indole intermediate is illustrated in Scheme 5. The commercially available bromoiodoaniline **5b**-1 may be coupled to the commercially available acetylene **5b**-1.1 under the Sonogashira conditions to give phenylacetylene **5b**-2. The latter may be cyclized to indole **5b**-3 under heat or microwave condition in the presence of a copper catalyst.



Scheme 5

In one aspect, the invention is a process of making a compound of Formula (**1-I**) comprising the steps of:

i) Preparing a compound of Formula (1-II-a):

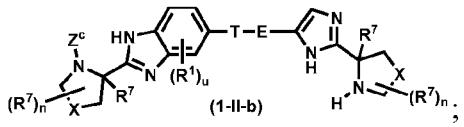


via a transition-metal catalyzed cross-coupling reaction; wherein:

E is optionally substituted aryl or optionally substituted heteroaryl; T, X, n, u, R^1, and R^7 are as defined in claim 1;

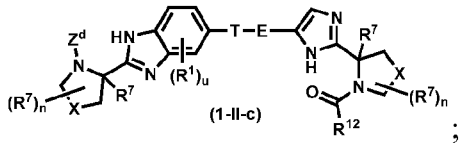
Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$; R^{12} is C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1$-C_4 alkyl);

ii) When Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (1-II-a) to give the corresponding amine of Formula (1-II-b):



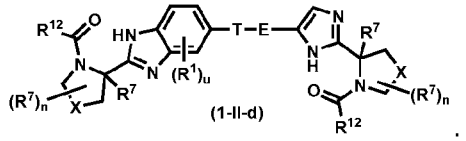
wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$;

iii) Capping the released amino group of a compound of Formula (1-II-b) with LG-C(O)-R^{12}, wherein LG is a leaving group; to give the compound of Formula (1-II-c):



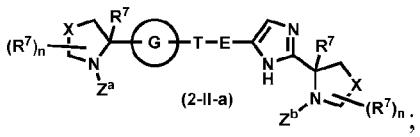
wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and

iv) Repeated reaction sequence of deprotecting and capping (step ii-iii) to give the compound of Formula (1-II-d):



In another aspect, the invention is a process of making a compound of Formula (**2-I**) comprising the steps of:

i. Preparing a compound of Formula (2-II-a):

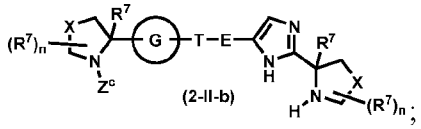


via a transition-metal catalyzed cross-coupling reaction; wherein:

E, G, T, X, n, u, v, R^1, and R^7 are as defined in claim 22;

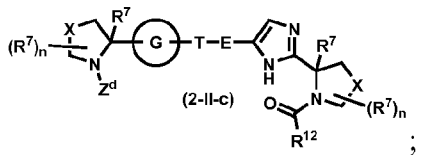
Z^a and Z^b are each independently an amino protecting group or $-C(O)-R^{12}$; R^{12} is C_1-C_8 alkyl optionally substituted with amino, hydroxy, protected amino, or $O(C_1$-C_4 alkyl);

ii. When Z^a or Z^b is an amino protecting group, fully or selectively deprotecting a compound of Formula (2-II-a) to give the corresponding amine of Formula (2-II-b):



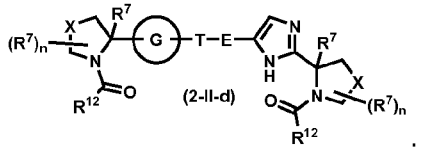
wherein Z^c is hydrogen, an amino protecting group or $-C(O)-R^{12}$;

iii. Capping the released amino group of a compound of Formula (2-II-b) with LG-C(O)-R^{12}, wherein LG is a leaving group; to give the compound of Formula (2-II-c):



wherein Z^d is an amino protecting group $-C(O)-R^{12}$; and

iv. Repeated reaction sequence of deprotecting and capping (step v-vii) to give the compound of Formula (2-II-d):



It will be appreciated that, with appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula **(1-I)** or **(2-I)** is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts "Protective Groups in Organic Synthesis", 3rd Ed (1999), J Wiley and Sons.

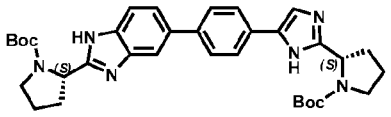
All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Although the invention has been described with respect to various preferred embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

Example 1-1.



Step 1-1a. A mixture of *N*-Boc-L-proline (5.754 g, 26.7 mmol) and TEA (3.73 mL, 26.7 mmol) in THF (60 mL) at −20 °C was treated with ethyl chloroformate (2.55 mL, 26.7 mmol) for 30 minutes before a slow addition of 4-bromo-1,2-diaminobenzene (5.00 g, 26.7 mmol) in THF (20 mL). It was then kept at −20 °C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a dark brown foam (10.7 g). ESIMS *m/z* = 384.18, 386.18 $[M+H]^+$.

Step 1-1b. A solution of the crude compound from step 1-1a (10.7 g, 26.7 mmol at most) in glacial acetic acid (100 mL) was heated at 50 °C for 2 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown foam (5.78 g, 59%). ESIMS *m/z* = 366.17, 368.17 $[M+H]^+$. ^1H NMR ($CDCl_3$) 10.96, 10.93 (2 s, 1H), 7.81, 7.30 (2 s, 1H), 7.53, 7.17 (2d, *J* = 8.5 Hz, 1H), 7.23, 7.03 (2d, *J* = 8.5 Hz, 1H), 5.09, 5.07 (2s, 1H), 3.42-3.49 (m, 2H), 2.75-2.85 (m, 1H), 2.13-2.23 (m, 2H), 1.97-2.00 (m, 1H), 1.48 (s, 9H).

Step 1-1c. A mixture of 2,4'-dibromoacetophenone (5.00 g, 18.0 mmol), *N*-Boc-L-proline (3.87 g, 18.0 mmol) and in CH_3CN (60 mL) was treated with TEA (5.40 mL, 37.8 mmol) at room temperature until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow foam (6.73 g, 91%). ^{1}H NMR ($CDCl_3$) 7.76 (t, J = 8.0 Hz, 2H), 7.63 (dd, J = 5.0, 8.5 Hz, 2H), 5.51, 5.16 (2d, J = 16.0 Hz, 1H), 5.32, 5.28 (2d, J = 16.5 Hz, 1H), 4.48, 4.40 (dd, J = 5.0, 8.5 Hz, 1H), 3.56 (m, 1H), 3.43 (m, 1H), 2.30 (m, 2H), 2.06 (m, 1H), 1.92 (m, 1H), 1.46, 1.43 (2s, 9H).

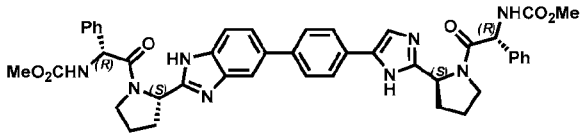
Step 1-1d. A solution of the compound from step 1-1c (6.73 g, 16.3 mmol) in toluene (100 mL) was treated with ammonium acetate (25.1 g, 0.327 mol) at 100 °C for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow foam (6.10 g, 95%). ESIMS *m/z* = 392.24, 394.24 $[M+H]^+$. ^{1}H NMR ($CDCl_3$) 7.57 (bs, 1H), 7.48 (m, 3H), 7.23 (s, 1H), 4.97 (m, 1H), 3.42 (m, 2H), 2.99 (m, 1H), 2.16 (m, 2H), 1.97 (m, 1H), 1.46 (s, 9H).

Step 1-1e. A mixture of the compound from step 1-1d (1.00 g, 2.55 mmol), bis(pinacolato) diboron (1.35 g, 5.33 mmol), $Pd(PPh_3)_4$ (0.147 g, 0.128 mmol) and potassium acetate (0.640 g, 6.53 mmol) in 1,4-dioxane (20 mL) was degassed and heated at 80 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow solid (0.978 g, 87%). ESIMS *m/z* = 440.39 $[M+H]^+$. ^{1}H NMR ($CDCl_3$) 11.03, 10.55 (2s, 1H), 7.79 (m, 3H), 7.45 (m, 1H), 7.26 (m, 1H), 4.97 (m, 1H), 3.41 (m, 2H), 3.06, 2.91 (2m, 1H), 2.17 (m, 2H), 1.97 (m, 1H), 1.49 (s, 9H), 1.35 (s, 12H).

Step 1-1f. A mixture of compound from step 1-1b (0.188 g, 0.512 mmol), the compound from step 1-1e (0.150 g, 0.342 mmol) $Pd(PPh_3)_4$, (39.4 mg, 34.1 μmol) and $NaHCO_3$ (0.115 g, 1.37 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 80 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried

(Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a white needle crystal (0.106 g, 52%). ESIMS *m/z* = 599.59 $[M+H]^+$.

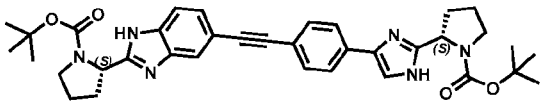
Example 1-2.



Step 1-2a. A solution of the compound of example 1-1 (20.0 mg, 33.4 μmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 399.35 $[M+H]^+$.

Step 1-2b. A mixture of the crude compound from step 1-2a (33.4 μmol at most) and (R)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 20.9 mg, 0.100 mmol) in DMF (3 mL) was treated with HATU (31.7 mg, 83.5 μmol) in the presence of DIPEA (83.0 μL, 0.668 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (23.8 mg, 2 steps 91%). ESIMS *m/z* = 781.67 $[M+H]^+$.

Example 1-1-1.

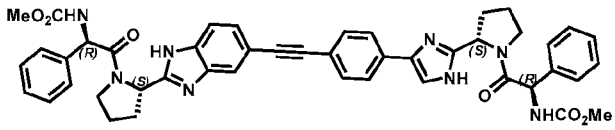


Step 1-1-1a. A mixture of the compound from step 1-1d (0.559 g, 1.425 mmol), trimethylsilyl-acetylene (0.60 ml, 4.275 mmol), CuI (28.5 mg, 0.150 mmol) and $Pd(PPh_3)_2Cl_2$ (80.0 mg, 0.114 mmol) in Et_3N (15 mL) was heated at 80 °C under N_2 for 6 hours before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow foam (0.484 g, 83%). ESIMS *m/z* = 410.24 $[M+H]^+$.

Step 1-1-1b. A suspension of the compound from step 1-1-1a (0.484 g, 1.182 mmol) and K_2CO_3 (0.408 g, 2.954 mmol) in methanol (12 ml) was stirred at rt for 3 hour. The volatiles were evaporated off. The residue was purified by chromatography (silica, dichloromethane-ethyl acetate) to give the desired compound as a yellow foam (0.370 g, 93%). ESIMS *m/z* = 338.24 $[M+H]^+$.

Step 1-1-1c. A mixture of the compound from step 1-1-1b (80.0 mg, 0.2371 mmol), the compound from step 1-1b (86.8 mg, 0.2371 mmol), CuI (2.2 mg, 0.01185 mmol) and $Pd(PPh_3)_2Cl_2$ (16.6 mg, 0.02371 mmol) in Et_3N (0.3 mL) and CH_3CN (2 mL) was heated at 85 °C under H_2/N_2 mixed gas for 2 hours before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow solid (48.3 mg, 33%). ESIMS m/z = 623.32 $[M+H]^+$.

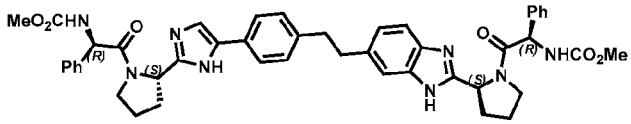
Example 1-2-1.



Step 1-2-1a. A solution of the compound of example 1-1-1 (48.3 mg, 0.0776 mmol) in 1,4-dioxane (1.5 mL) was treated with HCl in 1,4-dioxane (4 M, 6 mL) at rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step.

Step 1-2-1b. A mixture of the crude compound from step 1-2-1a (0.127 mmol at most) and (*R*)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 40.6 mg, 0.194 mmol) in DMF (1.5 mL) was treated with HATU (67.8 mg, 0.178 mmol) in the presence of DIPEA (0.27 mL, 1.551 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown syrup. It was purified by chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (36.2 mg, 2 steps 58%). ESIMS m/z = 805.29 $[M+H]^+$.

Example 1-2-2.

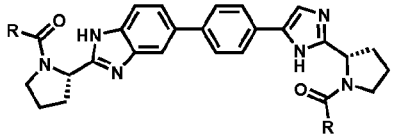


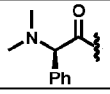
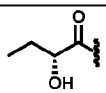
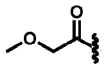
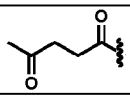
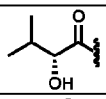
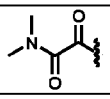
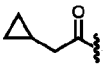
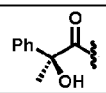
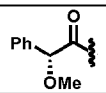
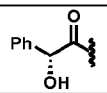
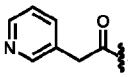
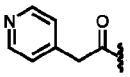
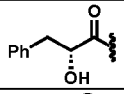
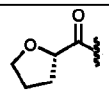
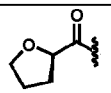
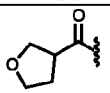
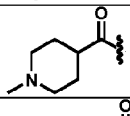
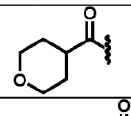
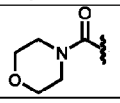
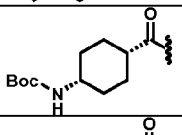
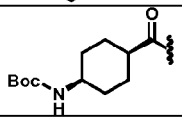
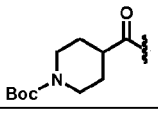
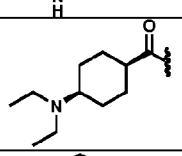
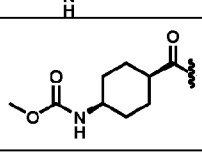
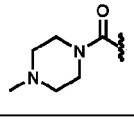
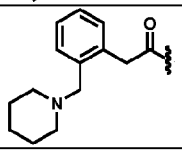
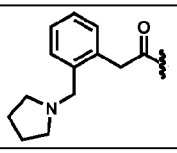
A solution of the compound of example 1-2-1 (23.0 mg, 0.0286 mmol) in ethanol (2 mL) was treated with $Pd(OH)_2$ (20wt% on carbon, 23 mg) at rt with a hydrogen balloon for 7 hourr. The mixture was filtered through a short pad of Celite. The volatiles were evaporated off. The residue was purified by chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a white solid (16.0 mg, 70%). ESIMS m/z = 809.40 $[M+H]^+$.

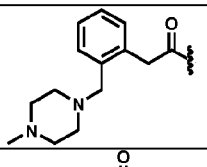
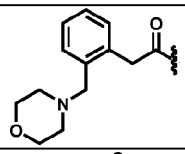
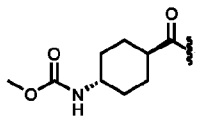
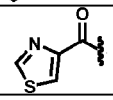
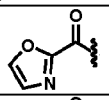
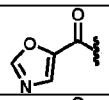
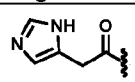
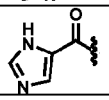
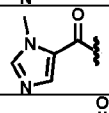
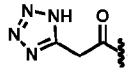
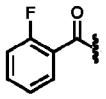
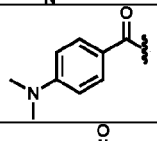
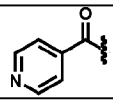
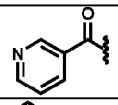
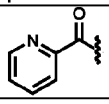
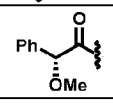
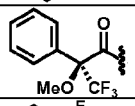
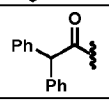
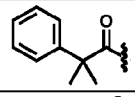
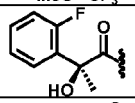
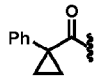
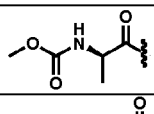
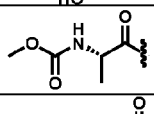
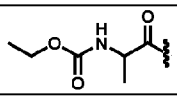
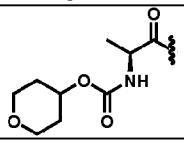
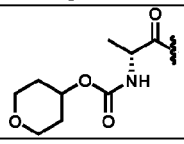
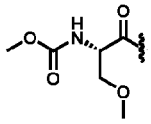
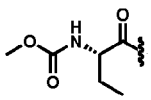
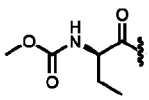
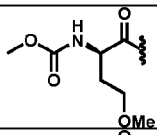
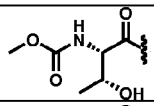
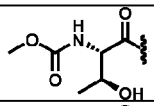
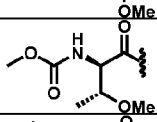
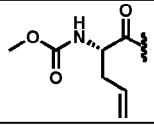
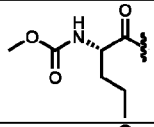
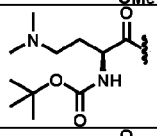
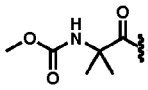
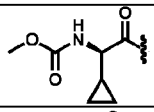
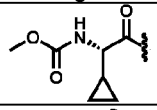
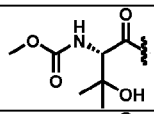
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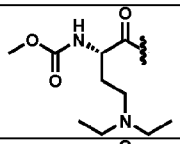
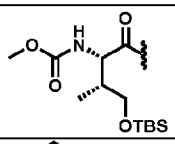
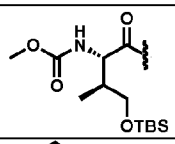
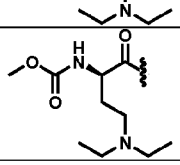
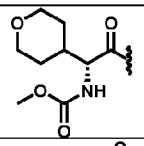
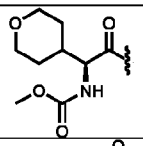
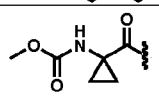
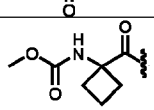
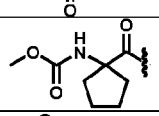
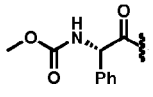
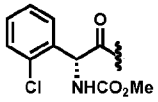
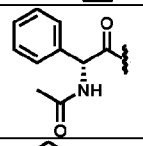
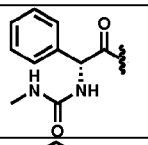
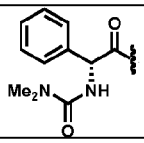
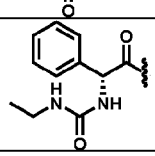
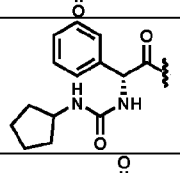
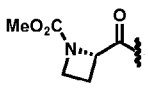
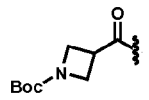
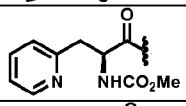
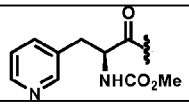
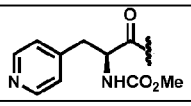
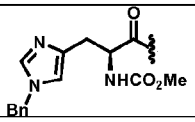
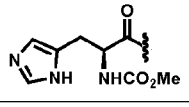
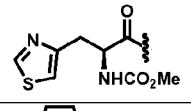
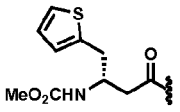
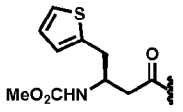
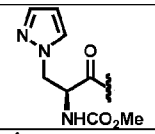
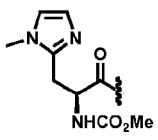
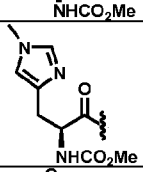
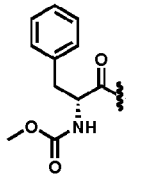
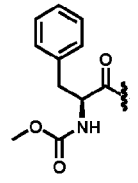
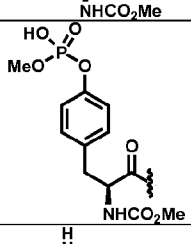
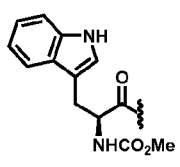
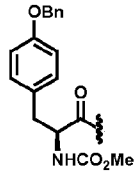
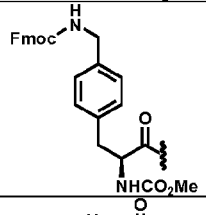
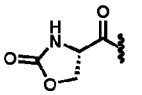
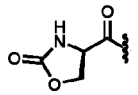
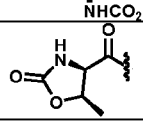
1-2-1, 1-2-2, 1-357, and 1-441 to 1-545, and/or as described in the Synthetic Methods.

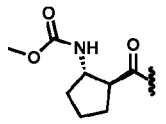
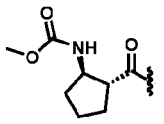
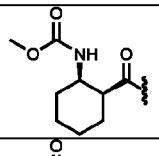
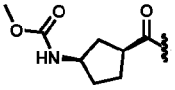
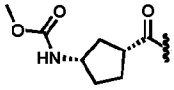
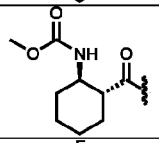
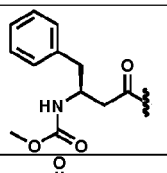
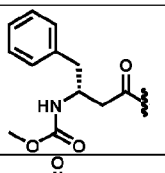
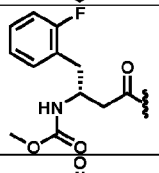
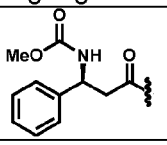
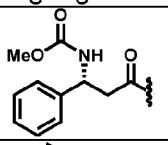
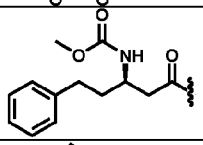
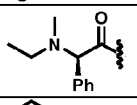
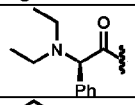
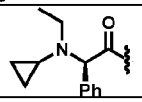
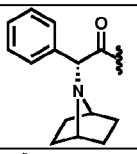
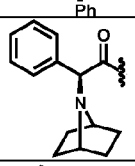
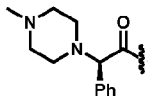
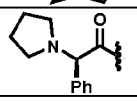
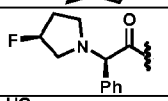
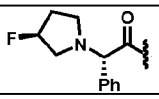
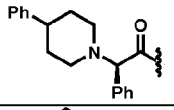
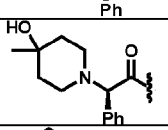
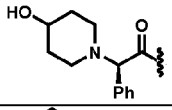
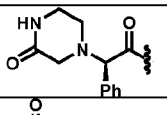
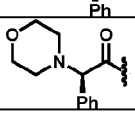
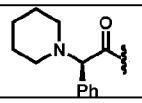
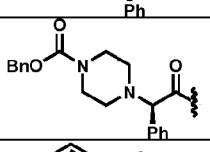
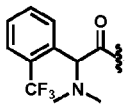
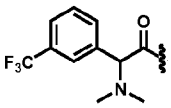
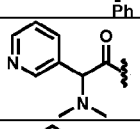
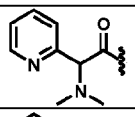
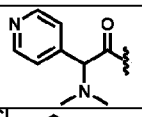
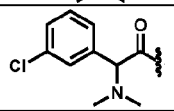
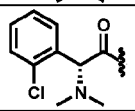
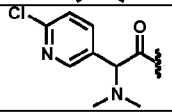
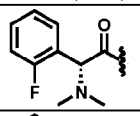
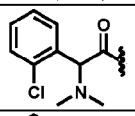
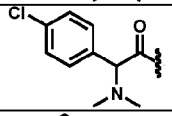
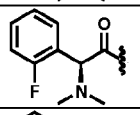
Table 1a: Examples 1-3 to 1-219.



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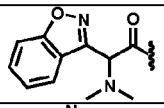
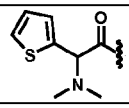
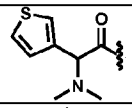
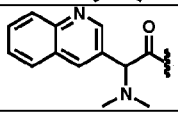
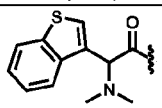
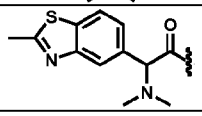
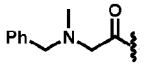
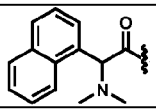
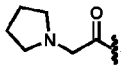
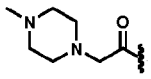
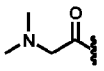
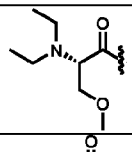
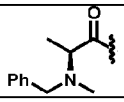
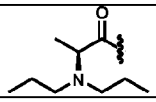
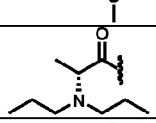
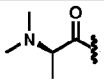
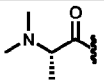
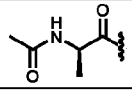
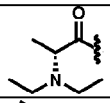
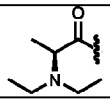
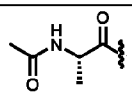
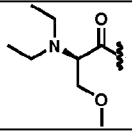
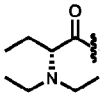
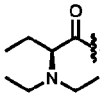
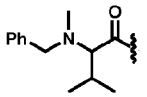
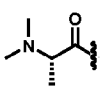
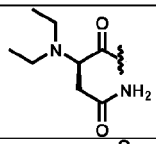
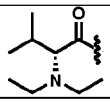
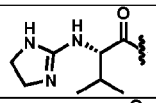
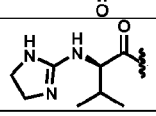
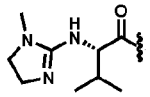
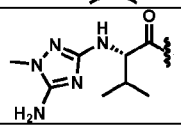
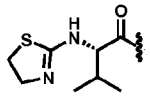
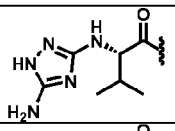
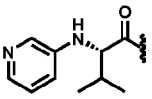
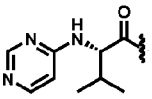
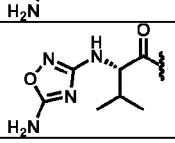
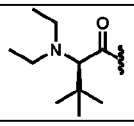
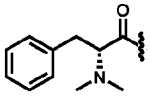
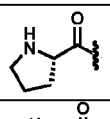
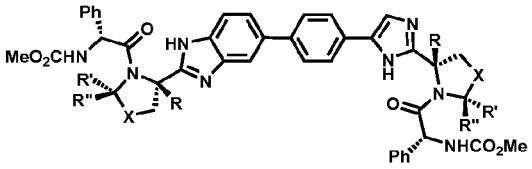
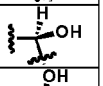
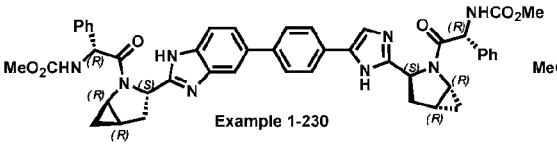
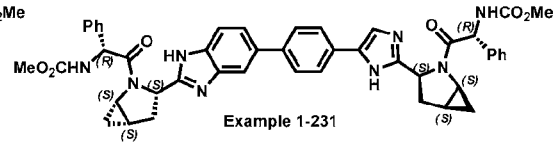
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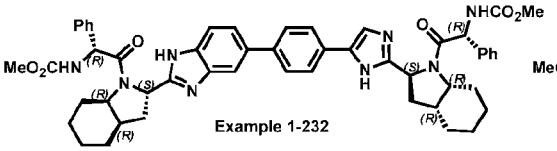
Table 2: Examples 1-220 to 1-229.



Entry 1-	R	R'	R"	X	Entry 1-	R	R'	R"	X
220	Me	H	H	CH_2	221	H	H	H	CF_2
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH_2	227	H	H	H	
228	H	H	Ph	CH_2	229	H	H	H	







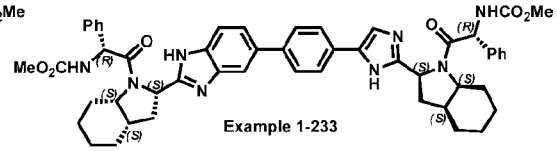
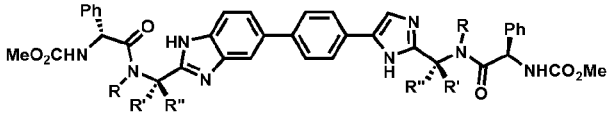
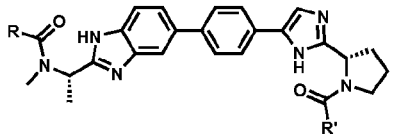


Table 3: Examples 1-234 to 1-243.



Entry 1-	R	R'	R"	Entry 1-	R	R'	R"
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	$CHMe_2$	H	243	Me	Et	H

Table 4: Examples 1-244 to 1-263.



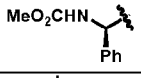
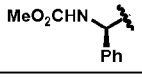
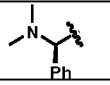
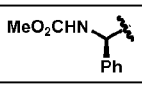
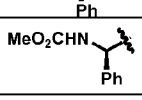
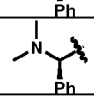
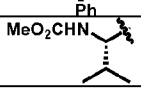
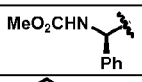
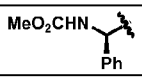
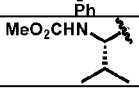
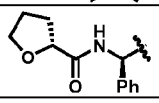
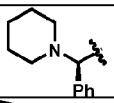
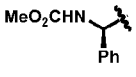
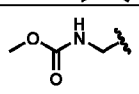
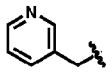
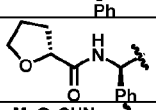
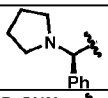
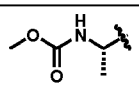
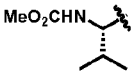
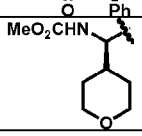
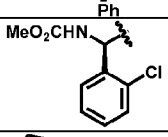
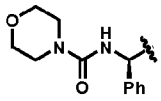
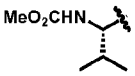
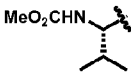
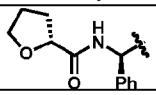
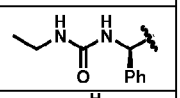
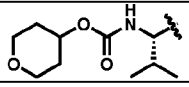
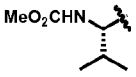
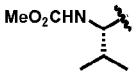
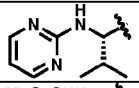
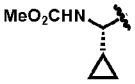
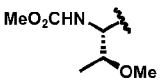
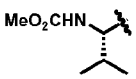
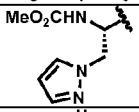
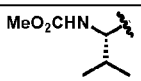
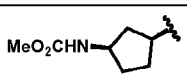
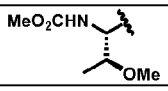
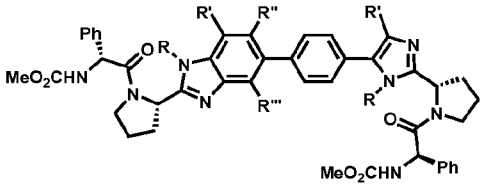
Entry 1-	R	R'	Entry 1-	R	R'
244			245		
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 5: Examples 1-264 to 1-273.

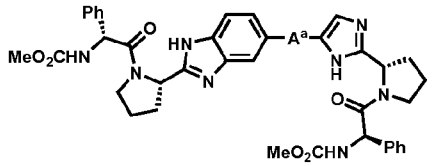
Entry 1-	R	R'	R''	R'''	Entry 1-	R	R'	R''	R'''
264	F	H	H	H	265	F	F	H	H
266	Me	H	H	H	267	Me	Me	H	H
268	H	H	Me	Me	269	H	H	Et	Et
270	CF_3	H	H	H	271	CF_3	H	CF_3	H
272	Cl	H	H	H	273	Cl	H	Cl	H

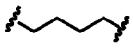
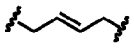
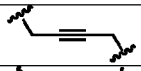
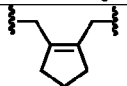
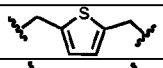
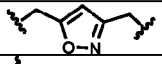
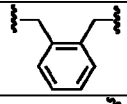
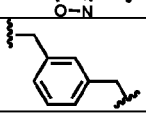
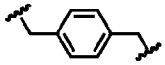
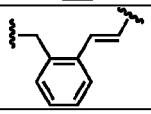
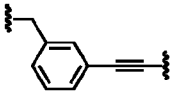
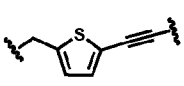
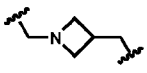
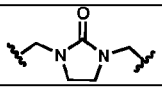
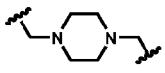
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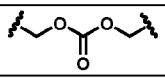
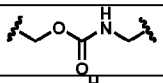
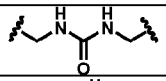
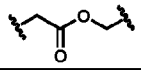
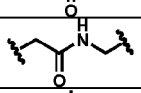
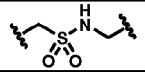
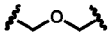
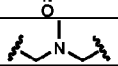
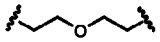
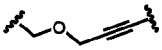
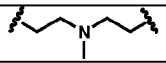
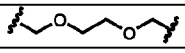
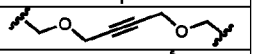
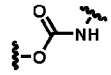
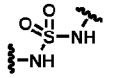
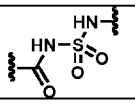
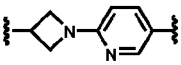
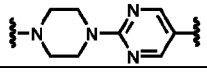
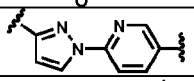
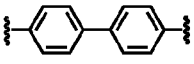
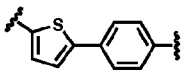
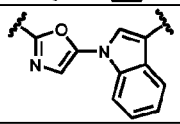
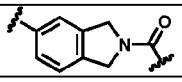
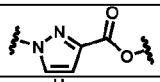
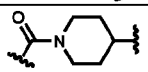
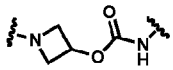
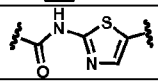
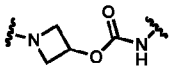
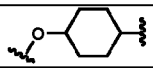
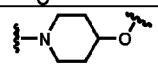
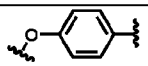
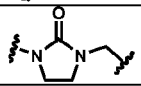
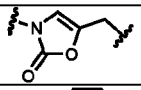
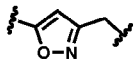
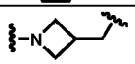
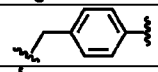
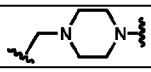
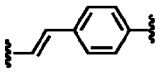


Entry 1-	R	R'	R"	R'"	Entry 1-	R	R'	R"	R'"
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276	H	F	H	H	277	H	H	CO_2H	H
278	H	H	F	H	279	H	H	H	CO_2H
280	H	H	H	F	281	H	CO_2Me	H	H
282	H	Cl	H	H	283	H	H	CO_2Me	H
284	H	H	Cl	H	285	H	H	H	CO_2Me
286	H	H	H	Cl	287	H	$CONH_2$	H	H
288	H	Me	H	H	289	H	H	$CONH_2$	H
290	H	H	Me	H	291	H	H	H	$CONH_2$
292	H	H	H	Me	293	H	OMe	H	H
294	H	CF_3	H	H	295	H	H	OMe	H
296	H	H	CF_3	H	297	H	H	H	OMe
298	H	H	H	CF_3	299	CO_2Me	H	H	H

Table 7: Examples 1-300 to 1-434.



Entry 1-	A^a	Entry 1-	A^a	Entry 1-	A^a
300		301		302	
303		304		305	
306		307		308	
309		310		311	
312		313		314	
315		316		317	

318		319		320	
321		322		323	
324		325		326	
327		328		329	
330		331		332	
333		334		335	
336		337		338	
339		340		341	
342		343		344	
345		346		347	
348		349		350	
351		352		353	
354		355		356	
357		358		359	
360		361		362	
363		364		365	
366		367		368	
369		370		371	
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384		385		386	
387		388		389	

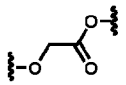
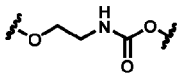
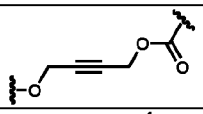
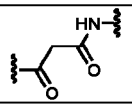
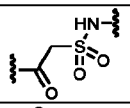
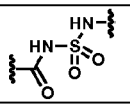
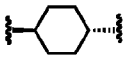
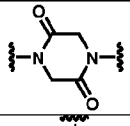
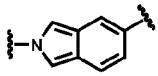
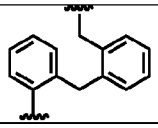
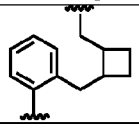
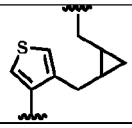
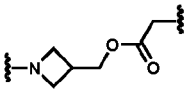
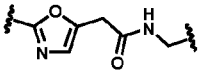
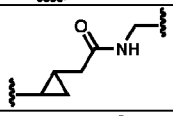
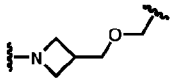
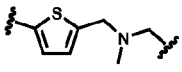
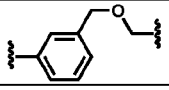
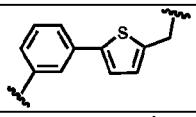
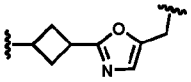
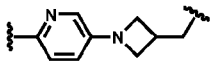
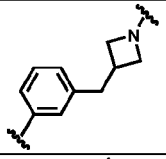
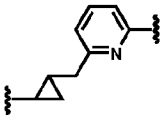
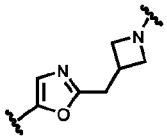
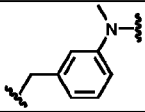
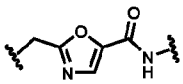
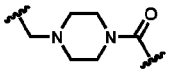
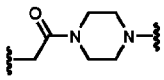
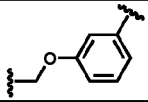
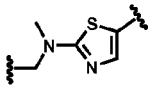
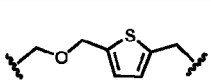
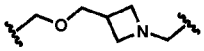
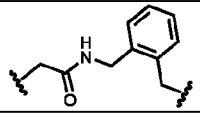
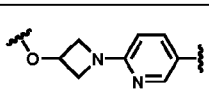
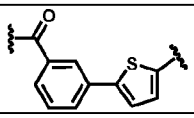
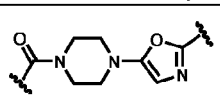
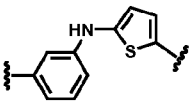
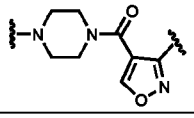
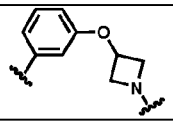
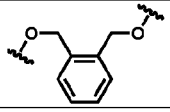
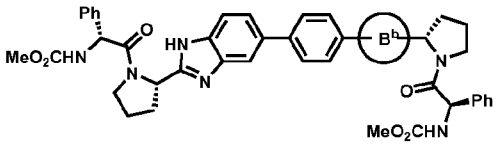
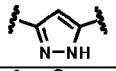
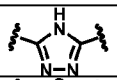
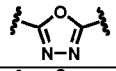
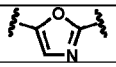
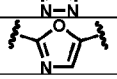
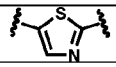
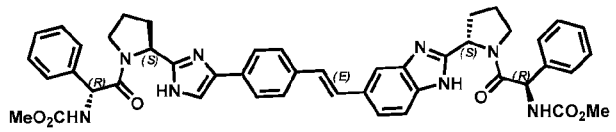
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423		424		425	
426		427		428	
429		430		431	
432		433		434	

Table 8: Examples 1-435 to 1-440.



Entry 1-	B^b	Entry 1-	B^b	Entry 1-	B^b
435		436		437	
438		439		440	

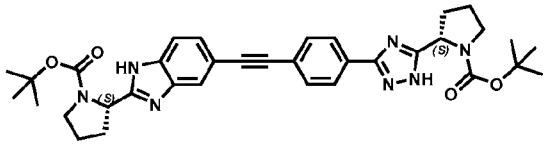
Example 1-357.



Step 1-357a. A solution of the compound of example 1-491 (0.122 g, 0.196 mmol) in 1,4-dioxane (2 mL) was treated with HCl in 1,4-dioxane (4 M, 8 mL) at rt for 1 hour. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step.

Step 1-357b. A mixture of the crude compound from step 1-357a (0.196 mmol at most) and (*R*)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 0.102 g, 0.490 mmol) in DMF (3 mL) was treated with HATU (0.171 g, 0.451 mmol) in the presence of DIPEA (0.68 mL, 3.920 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown syrup. It was patitioned (EtOAc - H_2O). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (0.144 g, 91% over 2 steps). ESIMS *m/z* = 806.96 $[M+H]^+$.

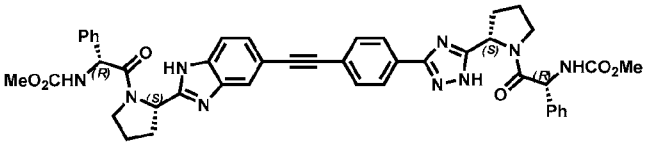
Example 1-441.



A mixture of (S)-tert-butyl 2-(3-(4-iodophenyl)-1H-1,2,4-triazol-5-yl)pyrrolidine-1-carboxylate (prepared according to US 2008/0311075, 84.9 mg, 0.193 mmol), the compound from step 1-515d (66.0 mg, 0.212 mmol), CuI (1.1 mg, 5.7 μmol) and $Pd(PPh_3)_2Cl_2$ (6.7 mg, 9.6 μmol) in CH_3CN (5 mL) and triethylamine (5 mL) was

degassed and heated to 50 °C under N_2 for 3 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow oil (94.0 mg, 78%). ESIMS *m/z* = 624.34 $[M+H]^+$.

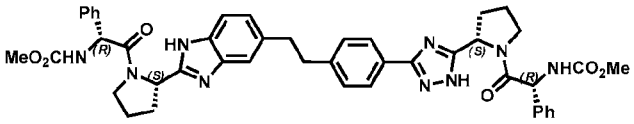
Example 1-442.



Step 1-442a. A solution of the compound of Example 1-441 (90.0 mg, 0.144 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 424.11 $[M+H]^+$.

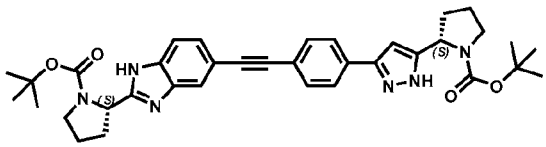
Step 1-442b. A mixture of the crude compound from step 1-442a (0.144 mmol at most) and (R)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 75.4 mg, 0.361 mmol) in DMF (3 mL) was treated with HATU (0.126 g, 0.332 mmol) in the presence of DIPEA (0.36 mL, 2.89 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a very light yellow solid (98.1 mg, 2 steps 80%). ESIMS *m/z* = 806.16 $[M+H]^+$.

Example 1-443.



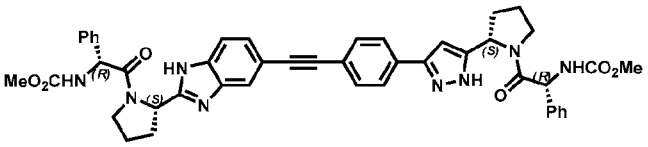
A mixture of the title compound of example 1-442 (51.6 mg, 63.3 μmol) and $Pd(OH)_2$ on carbon (20%, 50.0 mg) in ethanol (3 mL) was treated with H_2 balloon overnight. The mixture was filtered through celite and the filtrate was concentrated. The residue was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a white solid (42.5 mg, 82%). ESIMS *m/z* = 810.23 $[M+H]^+$.

Example 1-444.



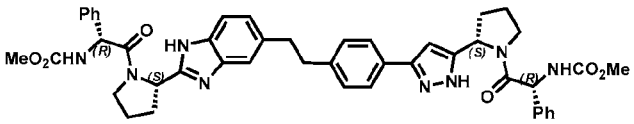
A mixture of (S)-tert-butyl 2-(3-(4-iodophenyl)-1H-pyrazol-5-yl)pyrrolidine-1-carboxylate (prepared according to US 2008/0311075, 85.0 mg, 0.213 mmol), the compound from step 1-515d (66.2 mg, 0.213 mmol), CuI (1.1 mg, 5.8 μmol) and $Pd(PPh_3)_2Cl_2$ (6.7 mg, 9.6 μmol) in CH_3CN (5 mL) and triethylamine (5 mL) was degassed and heated at 60 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow oil (91.1 mg, 76%). ESIMS *m/z* = 623.20 $[M+H]^+$.

Example 1-445.



The title compound was synthesized from the compound of Example 1-444 using procedures similar to that described in Example 1-442. ESIMS *m/z* = 805.36 $[M+H]^+$.

Example 1-446.



The title compound was synthesized from the compound of Example 1-445 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 809.42 $[M+H]^+$.

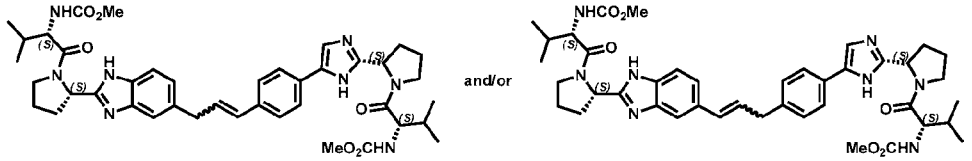
Example 1-447.



Step 1-447a. A mixture of the compound of step 1-1b (0.250 g, 0.683 mmol), allyltributyl-stannane (0.26 mL, 0.820 mmol) and $Pd(PPh_3)_4$ (39.4 mg, 34.1 μmol) in toluene (6 mL) was degassed and heated at 110 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a colorless oil (0.127 g, 60%). ESIMS *m/z* = 328.23 $[M+H]^+$.

Step 1-447b. A mixture of the compound of step 1-1d (0.180 g, 0.459 mmol), the compound of step 1-447a (0.150 g, 0.459 mmol), triethylamine (0.64 mL, 4.59 mmol), tri-*o*-tolylphosphine (18.0 mg, 57.3 μmol) and $Pd(OAc)_2$ (5.1 mg, 22.9 μmol) in CH_3CN (8 mL) was degassed and heated to 90 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compounds as a light yellow solid (0.165 g, 70%). The regio- and stereochemistry of the olefinic double bond was not determined. ESIMS *m/z* = 639.36 $[M+H]^+$.

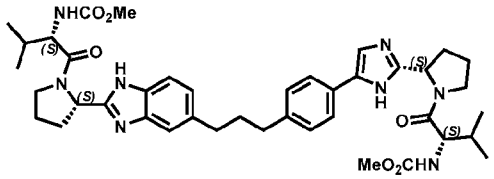
Example 1-448.



Step 1-448a. A solution of the compound of Example 1-447 (0.104 g, 0.163 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) at rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 439.24 $[M+H]^+$.

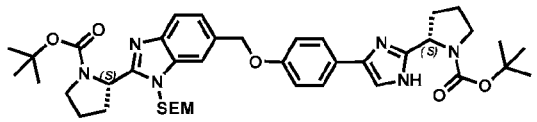
Step 1-448b. A mixture of the crude compound of step 1-448a (0.163 mmol at most) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (prepared according to WO 2008/021927, 71.3 mg, 0.408 mmol) in DMF (3 mL) was treated with HATU (0.142 g, 0.375 mmol) in the presence of DIPEA (0.41 mL, 3.26 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compounds as a white solid (89.5 mg, 2 steps 73%). The regio- and stereochemistry of the olefinic double bond was not determined. ESIMS *m/z* = 753.39 $[M+H]^+$.

Example 1-449.



The title compound was synthesized from the compound of Example 1-448 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 755.47 $[M+H]^+$.

Example 1-450.



Step 1-450a. The compound of step 1-1e (0.200 g, 0.455 mmol) in THF (5 mL) was treated with a mixture of 30% aqueous H_2O_2 (0.5 mL) and 1N aqueous NaOH (1 mL) for 30 minutes. The volatiles were removed and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (0.144 g, 96%). ESIMS *m/z* = 330.15 $[M+H]^+$.

Step 1-450b. The mixture of (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (5 g, 23.2 mmol) in acetonitrile (40 mL) was added 1,1′-carbonyldiimidazole (3.95 g, 24.5 mmol). The resulting mixture was stirred at room temperature for 20 min before being added methyl 3,4-diaminobenzoate (3.86g, 23.2 mmol). The solution was stirred at room temperature for another 3 hours before being partitioned between water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown slurry, which was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as a light yellow oil (8.14g, 98%). ESIMS *m/z* = 364.17 $[M+H]^+$.

Step 1-450c. The solution of compound from step 1-450b in acetic acid (150 mL) was stirred at 60 °C for three days before all volatiles were removed. The resulting residue was partitioned between aqueous $NaHCO_3$ and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil, which was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as a light yellow solid (2.02 g, 28%). ESIMS *m/z* = 346.15 $[M+H]^+$.

Step 1-450d. The solution of compound from step 1-450c (2.02g, 5.8 mmol) in DMF (50 mL) was added sodium hydride (55% in mineral oil, 269 mg, 6.4 mmol). The reaction was stirred at room temperature for 1.5 hours before being added 2-(Trimethylsilyl)ethoxymethyl chloride (1.02 mL, 5.8 mmol). The mixture was stirred at room temperature for another 3 hours before being partitioned between

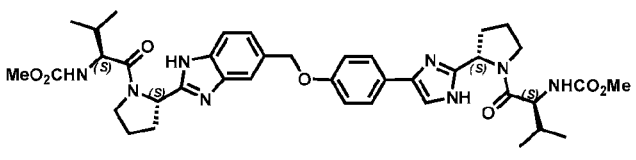
water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil, which was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as a light yellow solid (2.6g, 94%). ESIMS *m/z* = 475.97 $[M+H]^+$.

Step 1-450e. The solution of compound from step 1-450d (2.6g, 5.47 mmol) in THF (50 mL) and water (25 mL) was added lithium hydroxide monohydrate (690 mg, 16.4 mmol). The resulting mixture was stirred at room temperature for 3 hours before being partitioned between water, AcOH (10 mL) and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil, which was directly used for the next step without further purification (2.6 g, crude, 100%). ESIMS *m/z* = 462.02 $[M+H]^+$.

Step 1-450f. The solution of compound from step 1-450e (2.0g, 4.3 mmol) in THF (45 mL) was added triethylamine (1.85 mL, 12.9 mmol) and ethyl chloroformate (1.05 mL, 10.8 mmol) at 0 °C. The resulting mixture stirred at 0 °C for 20 minutes before all volatiles were removed by rotavap. The residue was dissolved in THF (70 mL) before being added sodium borohydride (1g, 26.4 mmol). The mixture was stirred at 0 °C for another 2 hours before being partitioned between water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil, which was purified by flash column chromatography (silica, EtOAc-methanol) to give the desired product as a light yellow solid (1.57g, 81%). ESIMS *m/z* = 448.13 $[M+H]^+$.

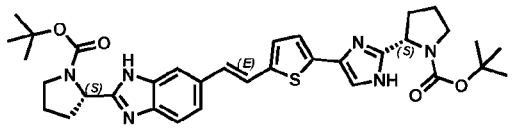
Step 1-450g. The compound from step 1-450a (70.0 mg, 0.213 mmol) in THF (5 mL) was treated with the compound from step 1-450f (95.1 mg, 0.213 mmol), PPh_3 (83.6 mg, 0.319 mmol) and DEAD (50.2 μL, 0.319 mmol) overnight before being evaporated to dryness. The residue was partitioned (EtOAc - water) and the organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a colorless oil (22.6 mg, 14%). The regiochemistry of the SEM group was not determined. ESIMS *m/z* = 759.39 $[M+H]^+$.

Example 1-451.



The title compound was synthesized from the compound of Example 1-450 using procedures similar to that described in steps 1-497a and 1-448b. ESIMS *m/z* = 743.32 $[M+H]^+$.

Example 1-452.



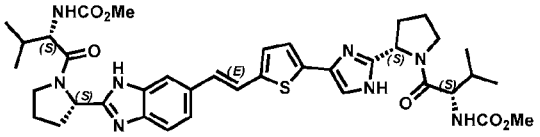
Step 1-452a. A mixture of 2-bromo-1-(5-bromothiophen-2-yl)ethanone (1.00 g, 3.52 mmol) and *N*-Boc-L-proline (0.758 g, 3.52 mmol) in CH_3CN (12 mL) was added TEA (1.06 mL, 7.40 mmol) slowly. The mixture was stirred at rt until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow sticky oil (1.47 g, 100%). ^1H NMR ($CDCl_3$) 7.49 (t, *J* = 4.0 Hz, 1H), 7.13 (dd, *J* = 4.5, 6.0 Hz, 1H), 5.36, 5.04 (2d, *J* = 16.0 Hz, 1H), 5.22, 5.15 (2d, *J* = 16.5 Hz, 1H), 4.45, 4.38 (dd, *J* = 5.5, 7.5 Hz, 1H), 3.56 (m, 1H), 3.41 (m, 1H), 2.25 (m, 2H), 2.05 (m, 1H), 1.90 (m, 1H), 1.46, 1.42 (2s, 9H).

Step 1-452b. A solution of the compound of step 1-452a (1.47 g, 3.52 mmol) in toluene (22 mL) was added ammonium acetate (5.42 g, 70.3 mmol) and the resultant mixture was heated at 100 °C for 16 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aq. $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown yellow foam (0.586 g, 42%) with a recovery of the compound from step 1-452a (0.616 g, 42%). ESIMS *m/z* = 398.16, 400.16 $[M+H]^+$. ^1H NMR ($CDCl_3$) 10.55 (bs, 1H), 7.07 (s, 1H), 6.94 (m, 2H), 4.92 (m, 1H), 3.40 (m, 2H), 2.96 (m, 1H), 2.12 (m, 2H), 1.92 (m, 1H), 1.49 (s, 9H).

Step 1-452c. A mixture of the compound of step 1-452b (0.150 g, 0.377 mmol), the compound from step 1-491a (0.118 g, 0.377 mmol), triethylamine (0.52 mL, 3.77 mmol), tri-*o*-tolyl-phosphine (14.8 mg, 47.1 μmol) and $Pd(OAc)_2$ (4.2 mg, 18.8 μmol) in CH_3CN (6 mL) was degassed and heated to 110 °C in sealed tube for 36 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4),

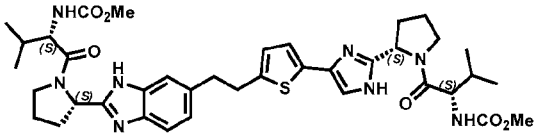
filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a yellow oil (64.1 mg, 27%). ESIMS *m/z* = 631.26 $[M+H]^+$.

Example 1-453.



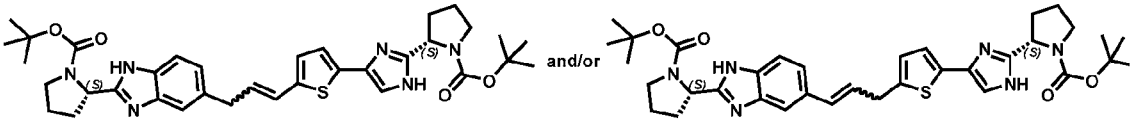
The title compound was synthesized from the compound from Example 1-452 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 745.43 $[M+H]^+$.

Example 1-454.



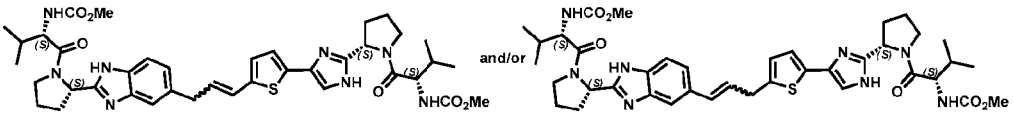
The title compound was synthesized from the compound from Example 1-453 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 747.40 $[M+H]^+$.

Example 1-455.



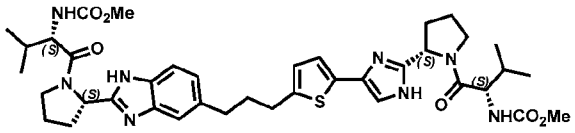
A mixture of the compound from step 1-452b (0.150 g, 0.377 mmol), the compound from step 1-447a (0.123 g, 0.377 mmol), triethylamine (0.52 mL, 3.77 mmol), tri-*o*-tolylphosphine (14.8 mg, 47.1 μmol) and $Pd(OAc)_2$ (4.2 mg, 18.8 μmol) in CH_3CN (6 mL) was degassed and heated to 110 °C in sealed tube for 36 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compounds as a yellow oil (52.7 mg, 22%). The regio- and stereochemistry of the olefinic double bond was not determined. ESIMS *m/z* = 645.27 $[M+H]^+$.

Example 1-456.



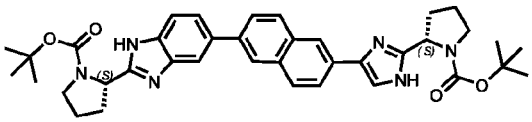
The title compound was synthesized from the compound from Example 1-455 using procedures similar to that described in Example 1-448. The regio- and stereochemistry of the olefinic double bond was not determined. ESIMS *m/z* = 759.51 $[M+H]^+$.

Example 1-457.



The title compound was synthesized from the compound from Example 1-456 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 761.41 $[M+H]^+$.

Example 1-458.



Step 1-458a. 6-bromo-N-methoxy-N-methyl-2-naphthamide (prepared according to *J. Med. Chem.*, 2006, *49*, 4721-4736, 3.57 g, 12.1 mmol) in THF (60 mL) was treated with methyl magnesium bromide (3M in Et_2O, 8.09 mL, 24.3 mmol) slowly at 0 °C for 1 hour. The solution was warmed up to rt for 2 hours before being quenched with aqueous NH_4Cl. The volatiles were removed and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a white solid (2.89 g, 96%).

Step 1-458b. The compound from step 1-458a (2.89 g, 11.6 mmol) in acetic acid (60 mL) was treated with bromine (0.59 mL, 11.6 mmol) dropwise for 1 hour. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a light yellow solid (3.898 g).

Step 1-458c. A mixture of the compound from step 1-458b (at most 11.6 mmol) and *N*-Boc-L-proline (3.75 g, 17.4 mmol) in CH_3CN (60 mL) was added DIPEA (2.89 mL, 23.2 mmol) slowly. The mixture was stirred at rt until the disappearence

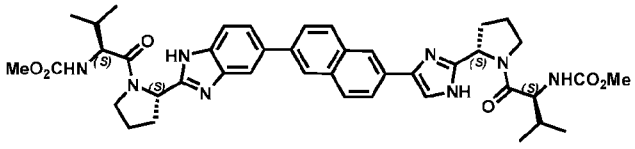
of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a yellow-white foam (4.762 g). ESIMS *m/z* = 462.03, 464.02 $[M+H]^+$.

Step 1-458d. A solution of the compound from step 1-458c (at most 11.6 mmol) in toluene (60 mL) was added ammonium acetate (13.4 g, 0.174 mol) and the resultant mixture was heated up at 100 °C for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aq. $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow brown powder (3.14 g, 4 steps, 61%). ESIMS *m/z* = 442.02, 444.02 $[M+H]^+$.

Step 1-458e. A mixture of the compound from step 1-1b (1 g, 2.73 mmol), bis-(pinacolato)-diboron (763 mg, 3.0 mmol), potassium acetate (402 mg, 4.0 mmol) in 1,4-dioxane (9.1 mL) was added tetrakis(triphenylphosphine)palladium(0) (158 mg, 0.14 mmol). The resulting solution was degased and then heated at 80 °C under N_2 overnight before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow solid (680 mg, 60%). ESIMS *m/z* = 414.24 $[M+H]^+$.

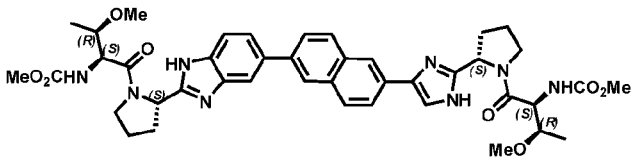
Step 1-458f. A mixture of the compound from step 1-458d (0.100 g, 0.226 mmol), the compound from step 1-458e (93.4 mg, 0.226 mmol), $Pd(PPh_3)_4$, (13.1 mg, 11.3 μmol) and $NaHCO_3$ (76.0 mg, 0.905 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 85 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (92.0 mg, 59%). ESIMS *m/z* = 649.54 $[M+H]^+$.

Example 1-459.



The title compound was synthesized from the compound from Example 1-458 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 763.21 $[M+H]^+$.

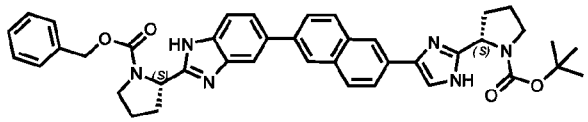
Example 1-460.



Step 1-460a. A solution of the compound of example 1-458 (92.0 mg, 0.142 mmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) rt for 30 minutes. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 449.39 $[M+H]^+$.

Step 1-460b. A mixture of the crude compound from step 1-460a (0.142 mmol at most) and (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (prepared according to WO 2008/021927, 56.9 mg, 0.298 mmol) in DMF (3 mL) was treated with HATU (0.108 g, 0.284 mmol) in the presence of DIPEA (0.35 mL, 2.84 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (60.3 mg, 2 steps 54%). ESIMS *m/z* = 795.68 $[M+H]^+$.

Example 1-461.



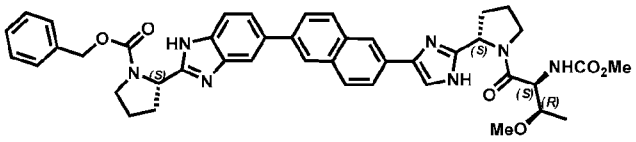
Step 1-461a. The desired compound was prepared from 4-bromo-1,2-diaminobenzene and *N*-Cbz-L-proline using procedures similar to that described in steps 1-1a and 1-1b. ESIMS *m/z* = 400.11, 402.11 $[M+H]^+$.

Step 1-461b. A mixture of the compound from step 1-461a (1.00 g, 2.50 mmol), bis(pinacolato)diboron (1.27 g, 5.00 mmol) and potassium acetate (0.613 g, 6.25 mmol) in 1,4-dioxane (25 mL) was added $Pd(PPh_3)_4$ (0.144 g, 0.125 mmol). The resultant mixture were degassed and heated up at 85 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow solid (0.801 g, 72%). ESIMS *m/z* = 448.18 $[M+H]^+$.

Step 1-461c. A mixture of the compound from step 1-458d (0.790 g, 1.79 mmol), the compound from step 1-461b (0.800 g, 1.79 mmol), $Pd(PPh_3)_4$, (0.103 g, 89.4

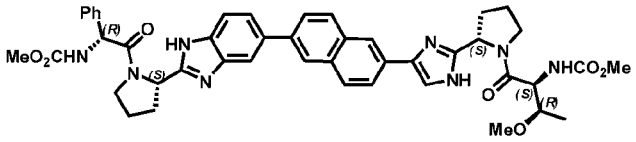
μmol) and $NaHCO_3$ (0.601 g, 7.16 mmol) in DME (24 mL) and H_2O (8 mL) was degassed and heated at 85 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (0.854 g, 70%). ESIMS *m/z* = 683.14 $[M+H]^+$.

Example 1-462.



The title compound was synthesized from the compound of Example 1-461 using procedures similar to that described in Example 1-460. ESIMS *m/z* = 756.26 $[M+H]^+$.

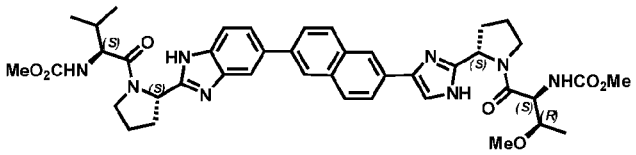
Example 1-463.



Step 1-463a. A mixture of the compound from example 1-462 (0.314 g, 0.416 mmol) and $Pd(OH)_2$ (20wt % on carbon, 150 mg) in methanol (6 mL) was adjusted pH to 3 with aqueous 6N HCl and then treated with hydrogen (60 psi) for 24 hours. The mixture was filtered through Celite and the filtrate was concentrated to give the crude desired compound as a light yellow solid (0.401 g). ESIMS *m/z* = 622.13 $[M+H]^+$.

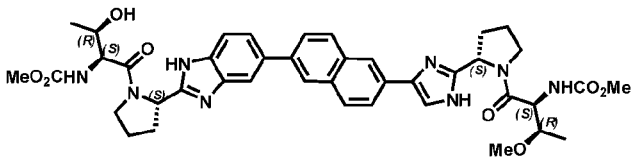
Step 1-463b. The title compound was synthesized from the compound from step 1-463a using procedures similar to that described in Example 1-442. ESIMS *m/z* = 813.32 $[M+H]^+$.

Example 1-464.



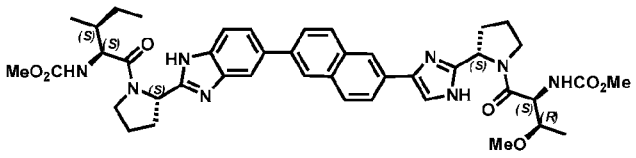
The title compound was synthesized from the compound of step 1-463a using procedures similar to that described in Example 1-448. ESIMS *m/z* = 779.33 $[M+H]^+$.

Example 1-465.



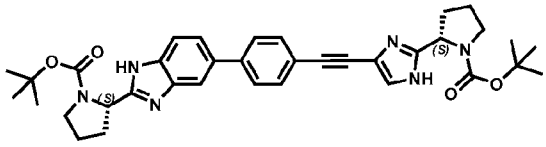
A mixture of the crude compound from step 1-463a (0.104 mmol at most) and (2S,3R)-3-hydroxy-2-(methoxycarbonylamino)butanoic acid (prepared according to WO 2008/021927, 20.2 mg, 0.114 mmol) in DMF (3 mL) was treated with HATU (35.5 mg, 93.5 μmol) in the presence of DIPEA (0.13 mL, 1.04 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow white solid (12.8 mg, 2 steps 16%). ESIMS *m/z* = 781.30 $[M+H]^+$.

Example 1-466.



A mixture of the crude compound from step 1-463a (0.104 mmol at most) and (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (prepared according to WO 2008/021927, 21.6 mg, 0.114 mmol) in DMF (3 mL) was treated with HATU (35.5 mg, 93.5 μmol) in the presence of DIPEA (0.13 mL, 1.04 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a light yellow solid (15.6 mg, 2 steps 19%). ESIMS *m/z* = 793.33 $[M+H]^+$.

Example 1-467.



Step 1-467a. (S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (prepared according to WO 2008/021927, 0.500 g, 1.58 mmol) in CH_2Cl_2 (16 mL) was treated with triethyl amine (0.66 mL, 4.75 mmol), di-tert-butyl dicarbonate (0.518 g, 0.237 mmol) and DMAP (38.7 mg, 0.316 mmol) for 1 hours before being evaporated to dryness. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a white solid (0.650 g, 98%). ESIMS *m/z* = 416.11, 418.11 $[M+H]^+$.

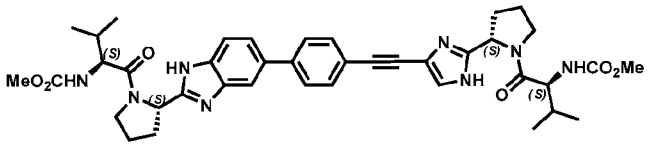
Step 1-467b. A mixture of the compound from step 1-467a (0.650 g, 1.56 mmol), ethynyl-trimethylsilane (2.16 mL, 15.6 mmol), CuI (8.9 mg, 46.8 μmol) and $Pd(PPh_3)_4$ (90.3 mg, 78.1 μmol) in CH_3CN (5 mL) and triethylamine (10 mL) was degassed and heated at 80 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (0.560 g, 83%). ESIMS *m/z* = 434.22 $[M+H]^+$.

Step 1-467c. The compound from step 1-467b (0.560 g, 1.29 mmol) in MeOH (30 mL) was treated with potassium carbonate (0.535 g, 3.88 mmol) for 30 minutes before being evaporated to dryness. The residue was partitioned (EtOAc - water), and the organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow solid (0.312 g, 92%). ESIMS *m/z* = 262.15 $[M+H]^+$.

Step 1-467d. A mixture of the compound from step 1-467c (0.103 g, 0.395 mmol), 1,4-diiodo-benzene (62.0 mg, 0.188 mmol), CuI (2.1 mg, 11.2 μmol) and $Pd(PPh_3)_4$ (21.6 mg, 18.7 μmol) in CH_3CN (1 mL) and triethylamine (4 mL) was degassed and heated to 60 °C under N_2 for 4 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a very light yellow solid (20.0 mg, 23%). ESIMS *m/z* = 464.06 $[M+H]^+$.

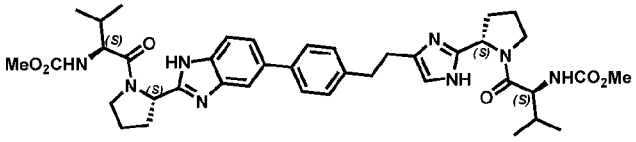
Step 1-467e. A mixture of the compound from step 1-467d (20.0 mg, 43.1 μmol), the compound from step 1-458e (17.8 mg, 43.1 μmol), $Pd(PPh_3)_4$, (9.9 mg, 8.6 μmol) and $NaHCO_3$ (14.5 mg, 0.172 mmol) in DME (3 mL) and H_2O (1 mL) was degassed and heated at 90 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (26.1 mg, 86%). ESIMS *m/z* = 623.28 $[M+H]^+$.

Example 1-468.



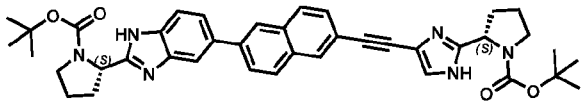
The title compound was synthesized from the compound of Example 1-467 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 737.26 $[M+H]^+$.

Example 1-469.



The title compound was synthesized from the compound of Example 1-468 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 741.23 $[M+H]^+$.

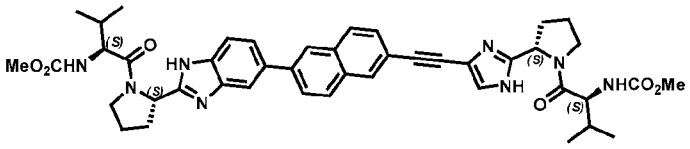
Example 1-470.



Step 1-470a. A mixture of the compound of step 1-467c (0.150 g, 0.575 mmol), 2,6-dibromo-naphthalene (98.6 mg, 0.345 mmol), CuI (3.3 mg, 17.2 μmol) and $Pd(PPh_3)_4$ (33.2 mg, 28.7 μmol) in CH_3CN (1 mL) and triethylamine (4 mL) was degassed and heated to 90 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a very light yellow oil (67.6 mg, 25%). ESIMS *m/z* = 466.00, 467.99 $[M+H]^+$.

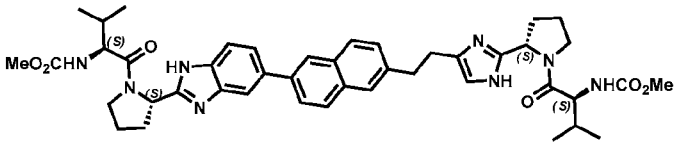
Step 1-470b. A mixture of the compound from step 1-470a (67.6 mg, 0.145 mmol), the compound from step 1-458e (59.9 mg, 0.145 mmol), $Pd(PPh_3)_4$, (16.8 mg, 14.5 μmol) and $NaHCO_3$ (48.7 mg, 0.580 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 90 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (78.8 mg, 81%). ESIMS *m/z* = 673.14 $[M+H]^+$.

Example 1-471.



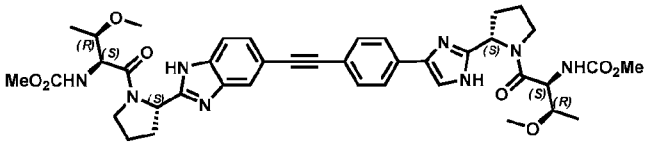
The title compound was synthesized from the compound of Example 1-470 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 787.26 $[M+H]^+$.

Example 1-472.



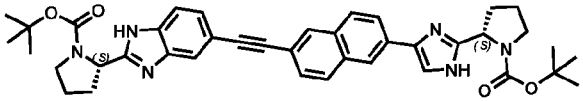
The title compound was synthesized from the compound of Example 1-471 using procedures similar to that described in Example 1-443. ESIMS *m/z* = 791.23 $[M+H]^+$.

Example 1-473.



The title compound was synthesized from the compound of Example 1-1-1 using procedures similar to that described in Example 1-460. ESIMS *m/z* = 769.37 $[M+H]^+$.

Example 1-474.

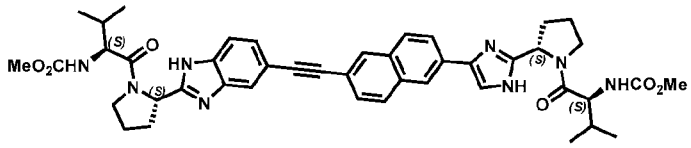


Step 1-474a. A mixture of the compound from step 1-515d (0.200 g, 0.643 mmol), 2,6-dibromonaphthalene (0.368 g, 1.29 mmol), CuI (3.6 mg, 19.2 μmol) and $Pd(PPh_3)_4$ (37.1 mg, 32.1 μmol) in CH_3CN (6 mL) and triethylamine (6 mL) was degassed and heated at 90 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (214 mg, 65%). ESIMS *m/z* = 516.08, 518.08 $[M+H]^+$.

Step 1-474b. A mixture of the compound from step 1-474a (0.214 g, 0.415 mmol), bis-(pinacolato) diboron (0.211 g, 0.829 mmol) and potassium acetate (0.102 g, 1.04 mmol) in 1,4-dioxane (8 mL) was added $Pd(PPh_3)_4$ (23.9 mg, 20.7 μmol). The resultant mixture were degassed and heated up at 85 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (0.163 g, 60% purity). ESIMS *m/z* = 564.17 $[M+H]^+$.

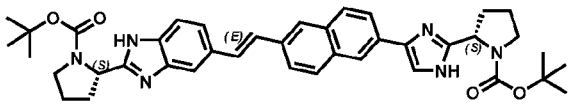
Step 1-474c. A mixture of the compound from step 1-474b (0.163 g, 0.290 mmol), (S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (prepared according to WO 2008/021927, 0.137 g, 0.434 mmol), $Pd(PPh_3)_4$, (33.4 mg, 28.9 μmol) and $NaHCO_3$ (97.2 mg, 1.16 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 90 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (0.122 g, 60% purity). ESIMS *m/z* = 673.29 $[M+H]^+$.

Example 1-475.



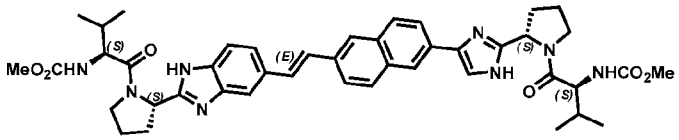
The title compound was synthesized from the compound from Example 1-474 using procedures similar to that described in Example 1-448 after HPLC purification. ESIMS *m/z* = 787.20 $[M+H]^+$.

Example 1-476.



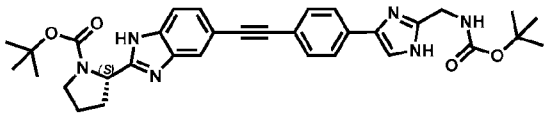
The title compound was obtained as an impurity in the compound of example 1-474. ESIMS *m/z* = 675.30 $[M+H]^+$.

Example 1-477.



The title compound was synthesized and purified as a minor product in example 1-475. ESIMS *m/z* = 789.21 $[M+H]^+$.

Example 1-478.

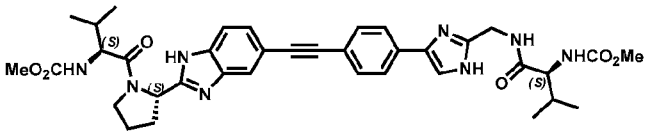


Step 1-478a. A mixture of 2,4'-dibromoacetophenone (1.59 g, 5.71 mmol) and *N*-Boc-glycine (1.00 g, 5.71 mmol) in CH_3CN (20 mL) was added DIPEA (1.42 mL, 11.4 mmol) slowly. The mixture was stirred at rt until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow solid (2.02 g, 95%). ESIMS *m/z* = 394.15, 396.15 $[M+Na]^+$.

Step 1-478b. A solution of the compound from step 1-478a (2.02 g, 5.43 mmol) in toluene (30 mL) was added ammonium acetate (8.35 g, 0.108 mol) and the resultant mixture was heated up at 100 °C for 20 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aq. $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to the desired compound as a yellow brown solid (1.62 g, 85%). ESIMS *m/z* = 352.14, 354.14 $[M+H]^+$.

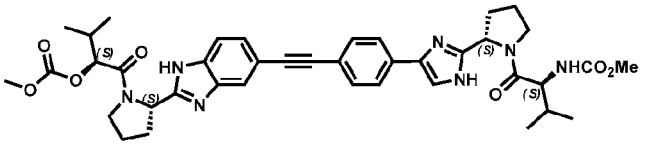
Step 1-478c. A mixture of the compound from step 1-478b (80.0 mg, 0.227 mmol), the compound from step 1-515d (77.8 mg, 0.250 mmol), CuI (1.3 mg, 6.8 μmol) and $Pd(PPh_3)_4$ (26.2 mg, 22.7 μmol) in triethylamine (6 mL) was degassed and heated at 85 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (50.9 mg, 39%). ESIMS *m/z* = 583.37 $[M+H]^+$.

Example 1-479.



The title compound was synthesized from the compound of Example 1-478 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 697.64 $[M+H]^+$.

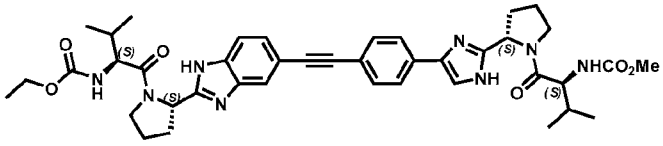
Example 1-480.



Step 1-480a. A solution of the compound of example 1-500 (10.0 mg, 14.7 μmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) rt for 30 min. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 580.55 $[M+H]^+$.

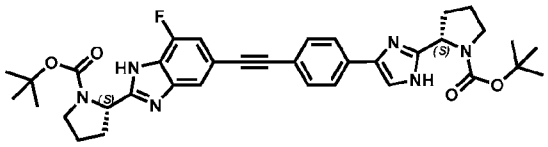
Step 1-480b. A mixture of the crude compound from step 1-480a (14.7 μmol at most) and (S)-2-(methoxycarbonyloxy)-3-methylbutanoic acid (prepared according to *Chemical & Pharmaceutical Bulletin*, **1985**, *33,* 3922-3928, 2.8 mg, 16.1 μmol) in DMF (3 mL) was treated with HATU (5.6 mg, 14.7 μmol) in the presence of DIPEA (37.0 μL, 0.294 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (8.3 mg, 2 steps 76%). ESIMS *m/z* = 738.64 $[M+H]^+$.

Example 1-481.



A mixture of the crude compound from step 1-480a (14.7 μmol at most) and (S)-2-(ethoxy-carbonylamino)-3-methylbutanoic acid (prepared according to WO 2008/021927, 3.0 mg, 16.1 μmol) in DMF (3 mL) was treated with HATU (5.6 mg, 14.7 μmol) in the presence of DIPEA (37.0 μL, 0.294 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a very yellow solid (10.2 mg, 2 steps 91%). ESIMS *m/z* = 751.67 $[M+H]^+$.

Example 1-482.

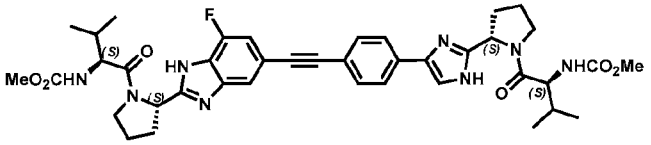


Step 1-482a. A mixture of *N*-Boc-L-proline (0.210 g, 0.976 mmol) and TEA (0.14 mL, 0.976 mmol) in THF (10 mL) at −20 °C was treated with *iso*-butyl chloroformate (0.13 mL, 0.976 mmol) for 30 minutes before a slow addition of 5-bromo-3-fluorobenzene-1,2-diamine (0.200 g, 0.976 mmol) in THF (2 mL). It was then kept at −20 °C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a brown foam (0.436 g). ESIMS *m/z* = 402.23, 404.23 $[M+H]^+$.

Step 1-482b. A solution of the crude compound from step 1-482a (0.976 mmol at most) in glacial acetic acid (10 mL) was heated at 65 °C for 24 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (0.327 g, 2 steps 87%). ESIMS *m/z* = 384.16, 386.16 $[M+H]^+$.

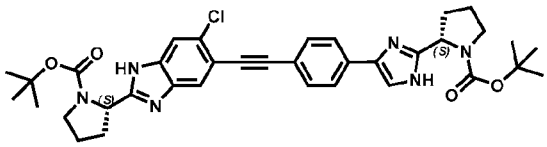
Step 1-482c. A mixture of the compound from step 1-482b (60.0 mg, 0.156 mmol), the compound from step 1-1-1b (58.0 mg, 0.172 mmol), CuI (0.9 mg, 4.6 μmol) and $Pd(PPh_3)_4$ (9.0 mg, 7.8 μmol) in triethylamine (4 mL) and CH_3CN (4 mL) was degassed and heated to 90 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (54.2 mg, 54%). ESIMS *m/z* = 641.22 $[M+H]^+$.

Example 1-483.



The title compound was synthesized from the compound of Example 1-482 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 755.55 $[M+H]^+$.

Example 1-484.



Step 1-484a. A mixture of 4-bromo-5-chlorobenzene-1,2-diamine (0.3 g, 1.19 mmol) and tin(II) chloride dihydrate (1.08 g, 4.77 mmol) in DMF (10 mL) was heated at 80 °C for 2 hours. The reaction was cooled and then neutralized by the addition of aqueous 2N NaOH. The resultant mixture were partitioned (EtOAc - water) and the organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow brown solid (0.256 g, 96%).

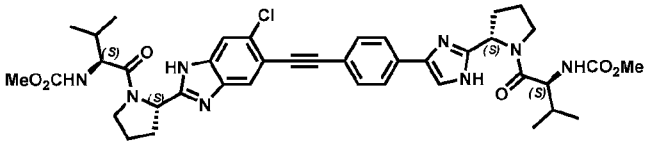
Step 1-484b. The compound from step 1-484a (0.250 g, 1.13 mmol) in DMF (10 mL) was treated with *N*-Boc-L-proline (0.243 g, 1.13 mmol), EDC·HCl (0.281 g, 1.47 mmol) and DMAP (27.6 mg, 0.226 mmol) for 12 hours before being partitioned (EtOAc - water). The organics were washed with aqueous 1N HCl, brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a light red brown foam (0.401 g). ESIMS *m/z* = 418.20, 420.20 $[M+H]^+$.

Step 1-484c. A solution of the crude compound from step 1-484b (1.13 mmol at most) in glacial acetic acid (10 mL) was heated at 50 °C for 2 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow brown solid (0.326 g, 2 steps 85%). ESIMS *m/z* = 400.21, 402.21 $[M+H]^+$.

Step 1-484d. A mixture of the compound from step 1-484c (55.0 mg, 0.140 mmol), the compound from step 1-1-1b (56.5 mg, 0.168 mmol), CuI (0.8 mg, 4.1 μmol) and $Pd(PPh_3)_4$ (8.0 mg, 6.9 μmol) in triethylamine (3 mL) and CH_3CN (3 mL) was degassed and heated to 95 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column

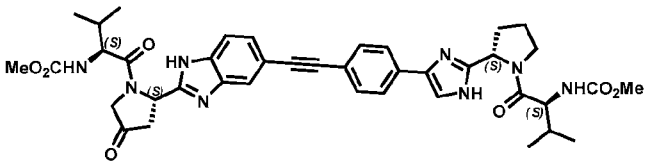
chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (49.7 mg, 55%). ESIMS *m/z* = 657.40 $[M+H]^+$.

Example 1-485.



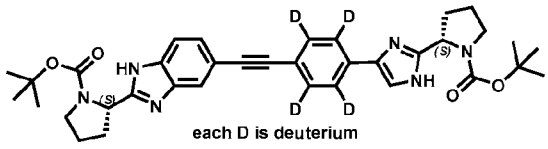
The title compound was synthesized from the compound of Example 1-484 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 771.63 $[M+H]^+$.

Example 1-486.



A solution the compound of example 1-517 (38.6 mg, 51.3 μmol) in CH_2Cl_2 (3 mL) was treated with camphorsulfonic acid (23.8 mg, 0.103 mmol) and Dess-Martin periodinane (0.131 mg, 0.308 mmol) for 5 hours before being quenched with satuated aqueous NsS_2O_3 and $NaHCO_3$. The mixture was partitioned (EtOAc - water) and the organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, MeOH-CH_2Cl_2) to give the title compound as a yellow brown solid (33.2 mg, 86%). ESIMS *m/z* = 751.54 $[M+H]^+$.

Example 1-487.



Step 1-487a. A solution of 4'-bromoacetophenone-d_7 (0.500 g, 2.43 mmol) in AcOH (10 mL) was treated with bromine (0.12 mL, 2.43 mmol) for 24 hours before being evaporated to dryness. The residue was partitioned (EtOAc - aqueous satuated $NaHCO_3$) and the organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the desired compound as a white crystal (0.672 g, 98%).

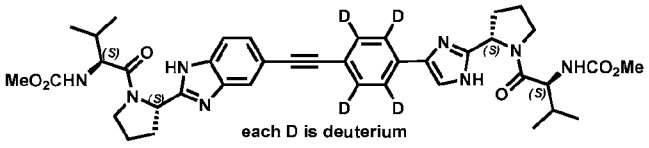
Step 1-487b. A mixture of the compound from step 1-487a (0.670 g, 2.38 mmol) and *N*-Boc-L-proline (0.511 g, 2.38 mmol) in CH_3CN (20 mL) was added DIPEA

(0.59 mL, 4.75 mmol) slowly. The mixture was stirred at rt until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a yellow brown oil (1.06 g). ESIMS *m/z* = 416.32, 418.32 $[M+H]^+$.

Step 1-487c. A solution of the compound from step 1-487b (at most 2.38 mmol) in toluene (24 mL) was added ammonium acetate (3.66 g, 47.5 mmol) and the resultant mixture was heated up at 100 °C for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aq. $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow brown powder (0.749 g, 2 steps, 78%). ESIMS *m/z* = 396.20, 398.20 $[M+H]^+$.

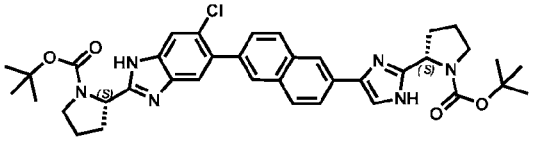
Step 1-487d. A mixture of the compound from step 1-487c (200 mg, 0.505 mmol), the compound from step 1-515d (0.188 g, 0.606 mmol), CuI (2.9 mg, 15.1 μmol) and $Pd(PPh_3)_4$ (29.1 mg, 25.2 μmol) in triethylamine (5 mL) and CH_3CN (5 mL) was degassed and heated at 95 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (0.151 g, 48%). ESIMS *m/z* = 627.58 $[M+H]^+$.

Example 1-488.



The title compound was synthesized from the compound from Example 1-487 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 741.70 $[M+H]^+$.

Example 1-489.

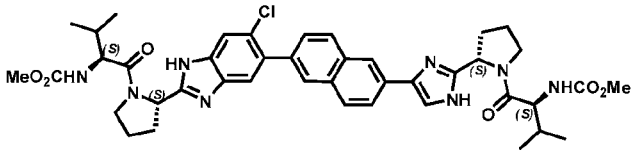


Step 1-489a. A mixture of the compound from step 1-458d (0.200 g, 0.452 mmol), bis(pinaco-lato)diboron (0.144 g, 0.565 mmol), $PdCl_2(dppf)_2$ (36.9 mg, 0.0452

mmol) and potassium acetate (88.7 mg, 0.904 mmol) in DMSO (5 mL) was degassed and heated at 80 °C under N_2 for 17 hours. The reaction mixture was allowed to cool down and partitioned (EtOAc - water). The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow solid (0.188 g, 85%). ESIMS *m/z* = 490.12 $[M+H]^+$.

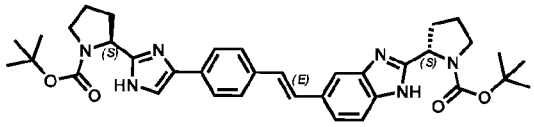
Step 1-489b. A mixture of the compound from step 1-484c (50.0 mg, 0.125 mmol), the compound from step 1-489a (73.2 mg, 0.150 mmol), $Pd(PPh_3)_4$, (7.2 mg, 6.2 μmol) and $NaHCO_3$ (41.9 mg, 0.499 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 95 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a white solid (21.3 mg, 25%). ESIMS *m/z* = 683.52 $[M+H]^+$.

Example 1-490.



The title compound was synthesized from the compound from Example 1-489 using procedures similar to that described in Example 1-448. ESIMS *m/z* = 797.62 $[M+H]^+$.

Example 1-491.

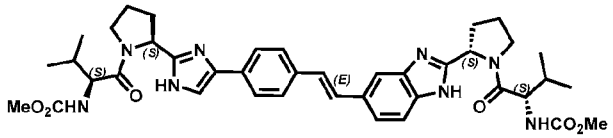


Step 1-491a. A mixture of the compound of step 1-1b (1.600 g, 4.369 mmol), tributyl(vinyl)-tin (1.53 ml, 5.242 mmol) and $Pd(PPh_3)_4$ (5 mol%, 0.250 g, 0.218 mmol) in toluene (20 mL) was degassed and then refluxed under N_2 for 18 h before being allowed to cool to rt. The mixture was directly purified by flash column chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a pink foam (0.912 g, 67%). ESIMS *m/z* = 314.18 $[M+H]^+$.

Step 1-491b. A mixture of the compound from step 1-491a (1.251 g, 3.191 mmol), the compound of step 1-1d (1.000 g, 3.191 mmol), $Pd(OAc)_2$ (5 mol%, 35.8 mg, 0.160 mmol) and P(*o*-tolyl)$_3$ (0.121 g, 0.399 mmol) in Et_3N (4.45 mL) and CH_3CN

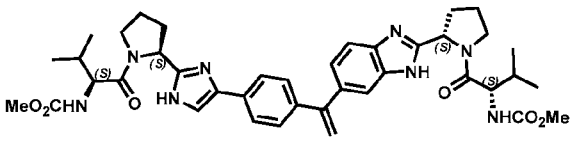
(30 mL) was degassed and refluxed under N_2 gas for 20 hours before being evaporated. The residue was taken up in dichloromethane and filtered through a short pad of Celite. The filtrate was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow solid (1.471 g, 74%). ESIMS *m/z* = 625.05 $[M+H]^+$.

Example 1-492.



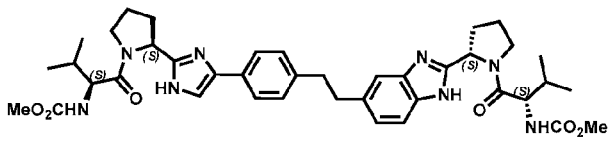
The title compound was prepared from the compound of example 1-491 using procedures similar to that described in example 1-448. ESIMS *m/z* = 739.15 $[M+H]^+$.

Example 1-493.



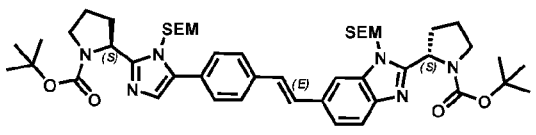
The title compound was obtained as a minor product (~ 2%) in example 1-492. ESIMS *m/z* = 739.03 $[M+H]^+$.

Example 1-494.



$Pd(OH)_2$ (20% on carbon, 10.8 mg) was added into a solution of the compound from example 1-492 (10.8 mg, 0.0146 mmol) in EtOH (1.5 mL). The suspension was purged with H_2 3 times and stirred at rt for 6 h under H_2 (60 psi) before being filtered through a short pad of Celite. The filtrate was concentrated. The crude was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a white solid (7.2 mg, 59%). ESIMS *m/z* = 741.13 $[M+H]^+$.

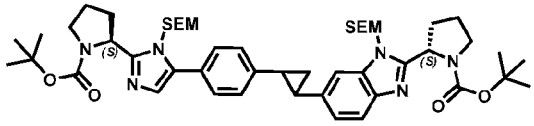
Example 1-495.



To a solution of the compound from example 1-491 (0.268 g, 0.430 mmol) in DMF (6 mL) was added NaH (60% in mineral oil, 36.0 mg, 0.902 mmol) at rt. The

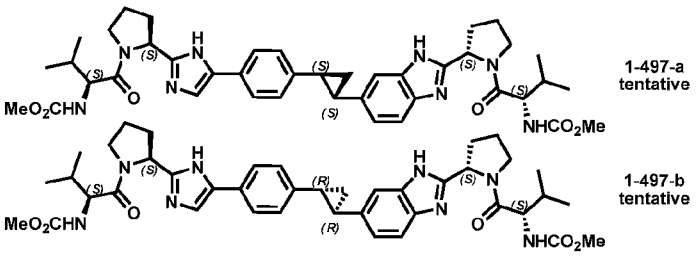
suspension was stirred at rt for 1 hour. SEMCl (0.154 mL, 0.868 mmol) was added dropwise at rt. After 1.5 hour at rt, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a yellow foam (0.290 g, 76%). The regiochemistry of the SEM groups was not determined. ESIMS *m/z* = 885.25 $[M+H]^+$.

Example 1-496.



To a solution of the compound from example 1-495 (0.150 g, 0.169 mmol) in THF (1.5 mL) was added $Pd(OAc)_2$ (3.8 mg, 0.0169 mmol) at 0 °C. Excess diazomethane (solution in ether) was added with a plastic pipette until the starting material was consumed. The suspension was concentrated. The residue was taken up in dichloromethane and filtered through a short pad of celite. The filtrate was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compounds as a colorless oil (0.106 g, 70%). The regiochemistry of the SEM group and the stereochemistry of the cyclopropyl ring were not determined. ESIMS *m/z* = 899.07 $[M+H]^+$.

Example 1-497.

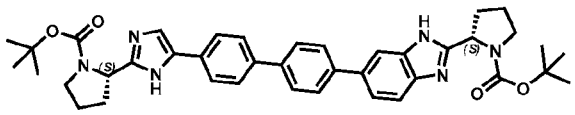


Step 1-497a. A solution of the compound of example 1-496 (0.106 g, 0.118 mmol) in 1,4-dioxane (2 mL) was treated with HCl in 1,4-dioxane (4 M, 12 mL) at 50 °C for 4 hour. The volatiles were evaporated off to give the crude desired compounds as a yellow solid which was used directly in the next step.

Step 1-497b. A mixture of the crude compound from step 1-497a (0.118 mmol at most) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (41.3 mg, 0.236 mmol) in DMF (3 mL) was treated with HATU (85.2 mg, 0.224 mmol) in the presence of DIPEA (0.41 mL, 2.360 mmol) for 1 hours at rt and the volatiles were

evaporated off to provide a brown syrup. The residue was patitioned (EtOAc - H_2O). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by RP-HPLC (NH_4HCO_3 buffer-MeOH) to give the title compounds: the major diastereomer (497-a, tentative) as a yellow solid (19.4 mg), ESIMS *m/z* = 753.12 $[M+H]^+$; and the minor diastereomer (497-b, tentative) as a yellow solid (3.1 mg), ESIMS *m/z* = 753.12 $[M+H]^+$. The stereochemistry of the cyclopropyl rings was not determined.

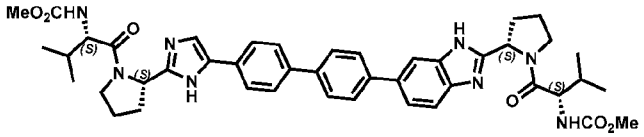
Example 1-498.



Step 1-498a. A mixture of the compound from step 1-458e (0.250 g, 0.605 mmol), 1-bromo-4-iodobenzene (0.257 g, 0.908 mmol), $NaHCO_3$ (0.203 g, 2.42 mmol) and $Pd(PPh_3)_4$ (34.9 mg, 30.2 μmol) in DME (12 mL) and water (4 mL) was degassed and heated to 85 °C under N_2 overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a very light yellow solid (0.246 g, 92%). ESIMS *m/z* = 442.00, 444.00 $[M+H]^+$.

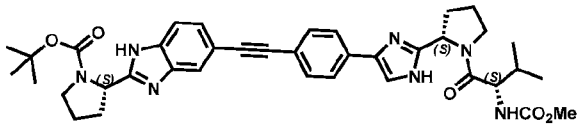
Step 1-498b. A mixture of the compound from step 1-1e (81.1 mg, 0.185 mmol), the compound from step 1-498a (85.8 mg, 0.194 mmol), $Pd(PPh_3)_4$, (21.4 mg, 18.5 μmol) and $NaHCO_3$ (62.1 mg, 0.739 mmol) in DME (3 mL) and H_2O (1 mL) was degassed and heated at 80 °C under N_2 for 22 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow solid (0.100 g, 81%). ESIMS *m/z* = 675.17 $[M+H]^+$.

Example 1-499.



The title compound was prepared from the compound of example 1-498 using procedures similar to that described in example 1-448. ESIMS *m/z* = 789.06 $[M+H]^+$.

Example 1-500.

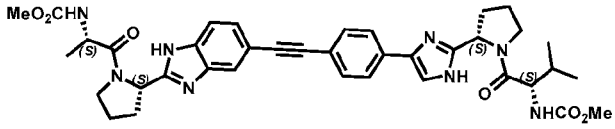


Step 1-500a. A solution of the compound from step 1-515b (2.000 g, 4.553 mmol) in 1,4-dioxane (25 mL) was treated with HCl in 1,4-dioxane (4 M, 50 mL) at rt for 1.5 hours. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step. ESIMS m/z = 339.89 $[M+H]^+$.

Step 1-500b. A mixture of the crude compound from step 1-500a (4.553 mmol at most) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.798 g, 4.553 mmol) in DMF (15 mL) was treated with HATU (1.644 g, 4.325 mmol) in the presence of DIPEA (7.93 mL, 45.53 mmol) for 1.5 hours at rt and the volatiles were evaporated off. The residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow foam (2.026 g, 90% over 2 steps). ESIMS m/z = 496.90 $[M+H]^+$.

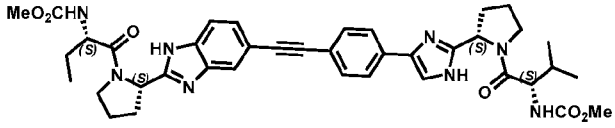
Step 1-500c. A mixture of compound from step 1-500b (0.800 g, 1.612 mmol), the compound from step 1-515d (0.501 g, 1.612 mmol), $Pd(PPh_3)_4$, (5 mol%, 93.1 mg, 80.6 μmol) and CuI (3 mol%, 9.2 mg, 48.3 μmol) in Et_3N (4 mL) and THF (12 mL) was degassed and stirred at 40 °C under N_2 for 18 hours. The volatiles were evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow solid (0.705 g, 64%). ESIMS m/z = 680.09 $[M+H]^+$.

Example 1-501.



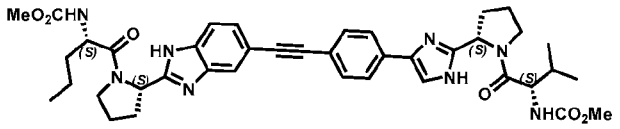
The title compound was prepared from the compound of example 1-500 and (*S*)-2-(methoxy-carbonylamino)propanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS m/z = 709.05 $[M+H]^+$.

Example 1-502.



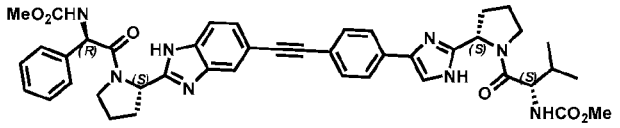
The title compound was prepared from the compound of example 1-500 and (*S*)-2-(methoxycarbonylamino)butanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 723.05 $[M+H]^+$.

Example 1-503.



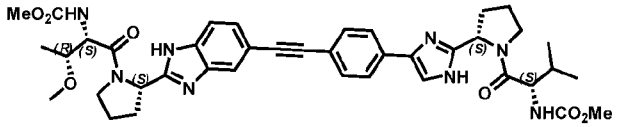
The title compound was prepared from the compound of example 1-500 and (*S*)-2-(methoxycarbonylamino)pentanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 737.09 $[M+H]^+$.

Example 1-504.



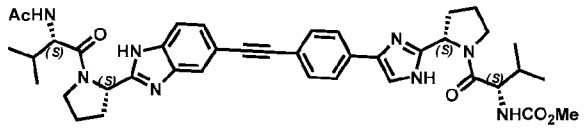
The title compound was prepared from the compound of example 1-500 and (*R*)-(methoxycarbonyl)amino phenyl acetic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 771.06 $[M+H]^+$.

Example 1-505.



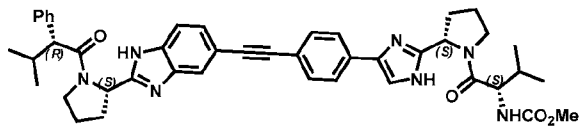
The title compound was prepared from the compound of example 1-500 and (2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 753.05 $[M+H]^+$.

Example 1-506.



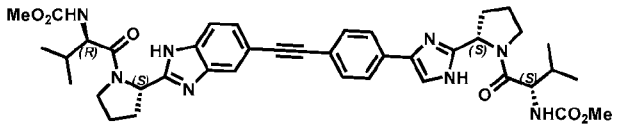
The title compound was prepared from the compound of example 1-500 and (*S*)-2-acetamido-3-methylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 721.48 $[M+H]^+$.

Example 1-507.



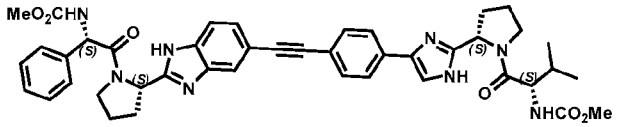
The title compound was prepared from the compound of example 1-500 and (*R*)-3-methyl-2-phenylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 740.50 $[M+H]^+$.

Example 1-508.



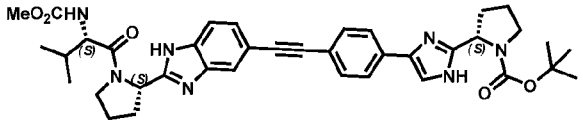
The title compound was prepared from the compound of example 1-500 and (*R*)-2-(methoxy-carbonylamino)-3-methylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 737.49 $[M+H]^+$.

Example 1-509.



The title compound was prepared from the compound of example 1-500 and (*S*)-2-(methoxy-carbonylamino)-2-phenylacetic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 771.40 $[M+H]^+$.

Example 1-510.

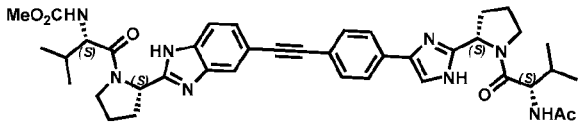


Step 1-510a. A solution of the compound fromthe compound from step 1-515d (1g, 3.21 mmol) in dichloromethane (20 mL) was treated with HCl in 1,4-dioxane (4 M, 12 mL) at room temperature for 1 hour. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step.

Step 1-510b. The mixture of compounds from step 1-510a (3.21 mml at most) and the compound from step 1-515g (562 mg, 3.21 mmol) in DMF (12 mL) was added diisopropylethylamine (4.56 mL, 32 mmol) and HATU (1.22g, 3.21 mmol). The resulting solution was stirred at room temperature for 1 hour before all volatiles were removed to provide a brown slurry, which was partitioned between EtOAc and aqueous NaOH (0.5M). The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil, which was purified by flash column chromatography (silica, EtOAc-methanol) to give the desired compound.

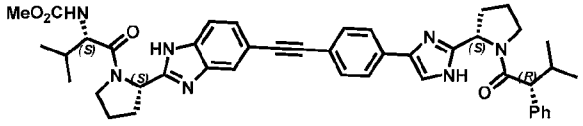
Step 1-510c. The title compound was prepared from the compound from step 1-510b and 1-515b using procedures similar to that described in step 1-500c. ESIMS *m/z* = 680.36 $[M+H]^+$.

Example 1-511.



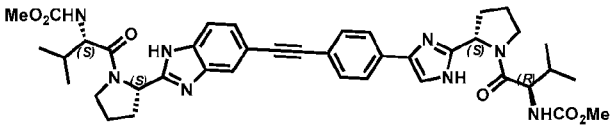
The title compound was prepared from the compound of example 1-510 and (*S*)-2-acetamido-3-methylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 721.49 $[M+H]^+$.

Example 1-512.



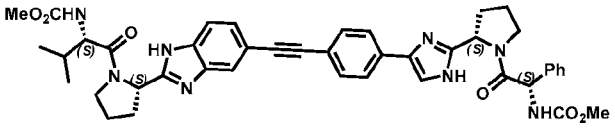
The title compound was prepared from the compound of example 1-510 and (*R*)-3-methyl-2-phenylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 740.51 $[M+H]^+$.

Example 1-513.



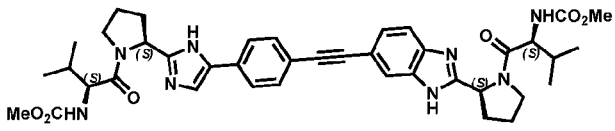
The title compound was prepared from the compound of example 1-510 and (*R*)-2-(methoxycarbonylamino)-3-methylbutanoic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 737.50 $[M+H]^+$.

Example 1-514.



The title compound was prepared from the compound of example 1-510 and (*S*)-2-(methoxycarbonylamino)-2-phenylacetic acid using procedures similar to that described in steps 1-500a and 1-500b. ESIMS *m/z* = 771.49 $[M+H]^+$.

Example 1-515.



Step 1-515a. Into a mixture of 2-bromo-1-(4-iodophenyl)ethanone (5g, 15.4 mmol) and (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (3.48g, 16.1 mmol) in acetonitrile (40 mL) was added diisopropylethylamine (2.4 mL, 17 mmol). The resulting mixture was stirred at rt for 3 hours before being partitioned between EtOAc and aqueous $NaHCO_3$. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown oil. It was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as light yellow oil (6.0 g, 86%). ESIMS *m/z* = 481.94 $[M+Na]^+$.

Step 1-515b. The mixture of compound from step 1-515a (6.0g, 12.5 mmol) and ammonium acetate (15.1g, 196 mmol) in toluene (80 mL) was stirred at 80 °C for 3 hours before being partitioned between water and aqueous $NaHCO_3$. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a deep red oil. It was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as light yellow solid (5.34 g, 93%). ESIMS *m/z* = 439.83 $[M+H]^+$.

Step 1-515c. A mixture of the compound from step 1-1b (2.010 g, 5.488 mmol), trimethyl-silylacetylene (2.33 ml, 16.46 mmol), CuI (0.110 g, 0.576 mmol) and $Pd(PPh_3)_2Cl_2$ (0.308 g, 0.439 mmol) in Et_3N (50 mL) was degased and then heated at 80 °C under N_2 overnight before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow foam (1.140 g, 54%). ESIMS *m/z* = 384.22 $[M+H]^+$.

Step 1-515d. A suspension of the compound from step 1-515c (1.140 g, 2.972 mmol) and K_2CO_3 (1.027 g, 7.430 mmol) in methanol (30 ml) was stirred at rt for 2 hour. The volatiles were evaporated off. The residue was patitioned (EtOAc - H_2O). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow foam (0.792 g, 86%). ESIMS *m/z* = 312.18 $[M+H]^+$.

Step 1-515e. The mixture of compounds from step 1-515b (9.1g, 20.7 mmol) and step 1-515d (6.45g, 20.7 mmol) in THF (200 mL), triethylamine (60 mL) and acetonitrile (200 mL) was added tetrakis(triphenylphosphine)palladium(0) (1.15g, 1 mmol) and copper(I) iodide (119 mg, 0.62 mmol). The resulting mixture was purged with nitrogen before being stirred at room temperature for 12 hours, at 50 °C for 2 hours and at 60 °C for 1 hour. After addition of aqueous NaOH (1M, 100 mL), the

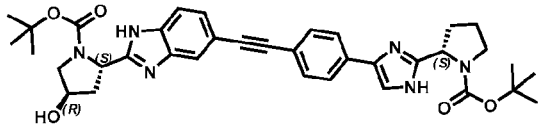
organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown slurry, which was absorbed with silica and purified by flash column chromatography (silica, EtOAc-methanol) to give the desired compound as light yellow solid (10.8 g, 84%). ESIMS *m/z* = 623.07 $[M+H]^+$.

Step 1-515f. A solution of the compound from step 1-515e (3g, 4.58 mmol) in dichloromethane (50 mL) and MeOH (5 mL) was treated with HCl in 1,4-dioxane (4 M, 40 mL) at rt for 2 hours. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step. ESIMS *m/z* = 423.06 $[M+H]^+$.

Step 1-515g. The mixture of L-valine (50g, 0.427 mol) in 1,4-dioxane (140 mL) was added water (630 mL), NaOH (54.7g, 1.4 mol) and methyl chloroformate (65.7 mL, 0.85 mol). The resulting solution was stirred at 60 °C for 22 hours before being added dichloromethane (400 mL). The aqueous phase was separated and extracted with dichloromethane (400 mL) before acidification with hydrochloric acid (37% in water, 90 mL). The cloudy suspension was extracted with EtOAc (500 mL) twice and the combined organic phases were dried (Na_2SO_4) and concentrated to afford a white solid, which was recrystalized with hexane and EtOAc to afford the desired product as colorless needle like crystals (54g, 72%). ^1H NMR (d^6-DMSO) 12.52 (s, 1H), 7.33 (d, 1H), 3.85 (dd, 1H), 3.56 (s, 3H), 2.06 (m, 1H), 0.98 (m, 6H).

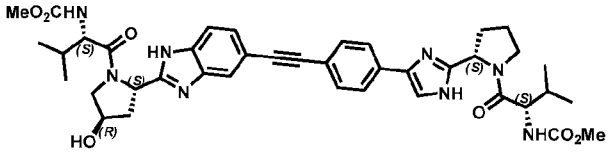
Step 1-515h. The mixture of compounds from step 1-515f (4.58 mml at most) and step 1-515g (1.61g, 9.16 mmol) in acetonitrile (50 mL) was added diisopropylethylamine (5.21 mL, 39 mmol) and HATU (3.31g, 8.7 mmol). The resulting solution was stirred at room temperature for 35 minutes before being partitioned between EtOAc (500 mL) and aqueous NaOH (0.5M, 50 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown slurry, which was purified by flash column chromatography (silica, EtOAc-methanol) to give the title compound as light yellow solid (2.31g, 65% over 2 steps). ESIMS *m/z* = 737.12 $[M+H]^+$.

Example 1-516.



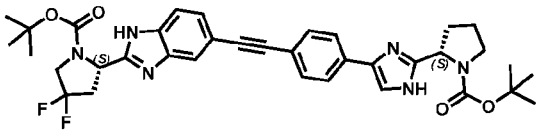
The title compound was prepared from (2S, 4R)-1-(tert-butoxycarbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid using procedures similar to that described in steps 1-515a to 1-515e. ESIMS *m/z* = 639.36 $[M+H]^+$.

Example 1-517.



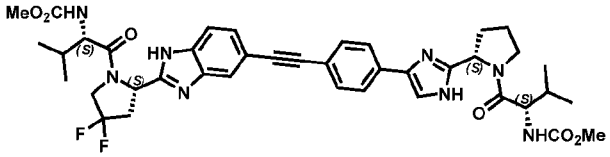
The title compound was prepared from the compound of example 1-516 using procedures similar to that described in example 1-448. ESIMS *m/z* = 753.46 $[M+H]^+$.

Example 1-518.



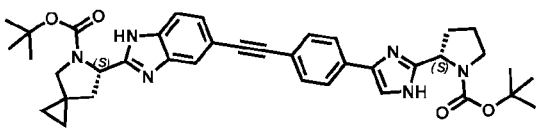
The title compound was prepared from (2S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid using procedures similar to that described in steps 1-515a to 1-515e. ESIMS *m/z* = 659.35 $[M+H]^+$.

Example 1-519.



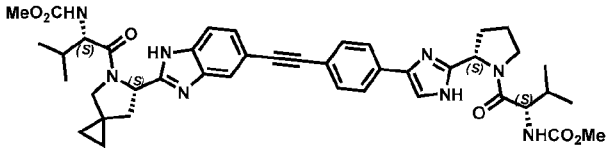
The title compound was prepared from the compound of example 1-518 using procedures similar to that described in example 1-448. ESIMS *m/z* = 773.34 $[M+H]^+$.

Example 1-520.



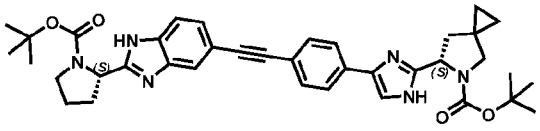
The title compound was prepared from the compound from step 1-1-1b, 4-bromo-1,2-diaminobenzene and (6*S*)-5-[(*tert*-butoxy)carbonyl]-5-azaspiro[2.4]heptane-6-carboxylic acid (prepared according to WO 2009/102325) using procedures similar to that described in examples 1-1 and 1-1-1. ESIMS *m/z* = 649.30 $[M+H]^+$.

Example 1-521.



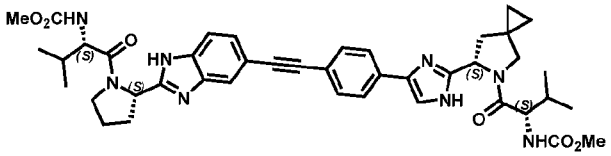
The title compound was prepared from the compound of Example 1-521 using procedures similar to that described in example 1-448. ESIMS *m/z* = 763.30 $[M+H]^+$.

Example 1-522.



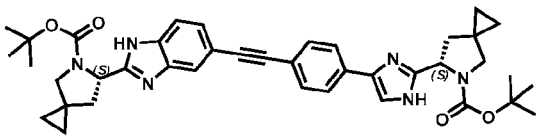
The title compound was prepared from 2,4'-dibromoacetophenone, the compound from step 1-515d and (6*S*)-5-[(*tert*-butoxy)carbonyl]-5-azaspiro[2.4]heptane-6-carboxylic acid (prepared according to WO 2009/102325) using procedures similar to that described in examples 1-1 and 1-515. ESIMS *m/z* = 649.35 $[M+H]^+$.

Example 1-523.



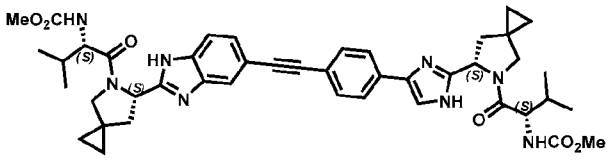
The title compound was prepared from the compound of Example 1-522 using procedures similar to that described in example 1-448. ESIMS *m/z* = 763.44 $[M+H]^+$.

Example 1-524.



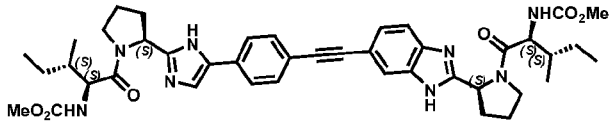
The title compound was prepared from 2,4'-dibromoacetophenone, 4-bromo-1,2-diamino-benzene and (6*S*)-5-[(*tert*-butoxy)carbonyl]-5-azaspiro[2.4]heptane-6-carboxylic acid (prepared according to WO 2009/102325) using procedures similar to that described in examples 1-1 and 1-515. ESIMS *m/z* = 675.35 $[M+H]^+$.

Example 1-525.



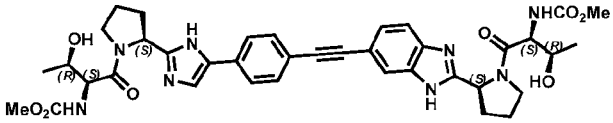
The title compound was prepared from the compound of Example 1-524 using procedures similar to that described in example 1-448. ESIMS *m/z* = 789.47 $[M+H]^+$.

Example 1-526.



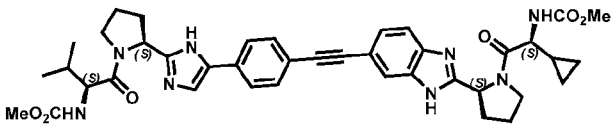
A mixture of the crude compound from step 1-515f (0.105 mmol at most) and (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid (prepared by procedure similar to that in step 515g, 35 mg, 0.21 mmol) in acetonitrile (2 mL) was treated with HATU (79 mg, 0.21 mmol) in the presence of DIPEA (0.15 mL, 1.05 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (60 mg, 2 steps 75%). ESIMS *m/z* = 765.14 $[M+H]^+$.

Example 1-527.



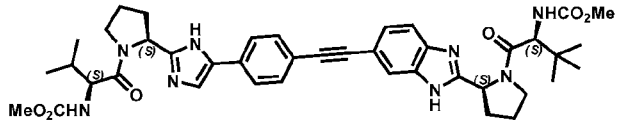
A mixture of the crude compound from step 1-515f (0.10mmol at most) and (2S,3R)-3-hydroxy-2-(methoxycarbonylamino)butanoic acid (prepared by procedure similar to that described in step 1-515g, 35 mg, 0.20 mmol) in DMF (2 mL) was treated with HATU (76 mg, 0.20 mmol) in the presence of DIPEA (0.12 mL, 0.80 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (64 mg, 2 steps 86%). ESIMS *m/z* = 741.07 $[M+H]^+$.

Example 1-528.



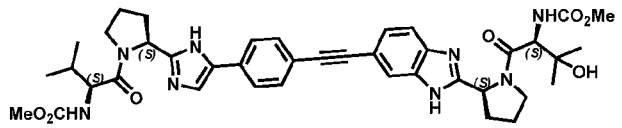
A mixture of the crude compound from step 1-480a (0.015 mmol at most) and (S)-2-cyclopropyl-2-(methoxycarbonylamino) acetic acid (prepared by procedure similar to that described in step 1-515g, 2.6 mg, 0.015 mmol) in acetonitrile (2 mL) was treated with HATU (5.7 mg, 0.015mmol) in the presence of DIPEA (0.03 mL, 0.15 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown oil. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (7.6 mg, 2 steps 69%). ESIMS *m/z* = 735.22 $[M+H]^+$.

Example 1-529.



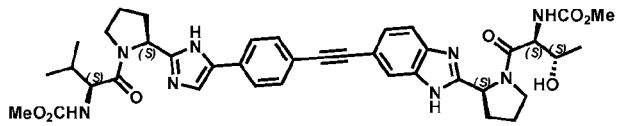
The title compound as a yellow solid (7.9 mg, 2 steps 71%) was prepared from the crude compound from step 1-480a (0.015 mmol at most) and (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (2.8 mg, 0.015 mmol) using the procedures similar to that described in example 1-528. ESIMS *m/z* = 751.55 $[M+H]^+$.

Example 1-530.



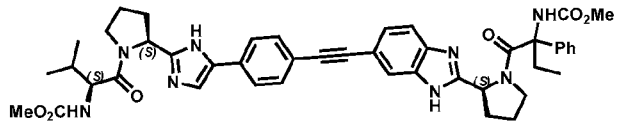
The title compound as a yellow solid (7.3 mg, 2 steps 65%) was prepared from the crude compound from step 1-480a (0.015 mmol at most) and (S)-3-hydroxy-2-(methoxycarbonyl-amino)-3-methylbutanoic acid (2.8 mg, 0.015 mmol) using the procedures similar to that described in example 1-528. ESIMS *m/z* = 753.36 $[M+H]^+$.

Example 1-531.



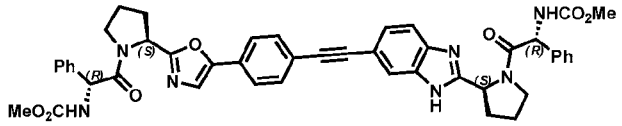
The title compound as a yellow solid (4.0 mg, 2 steps 36%) was prepared from the crude compound from step 1-480a (0.015 mmol at most) and (2S,3S)-3-hydroxy-2-(methoxy-carbonylamino)butanoic acid (2.6 mg, 0.015 mmol) using the procedures similar to that described in example 1-528. ESIMS *m/z* = 739.26 $[M+H]^+$.

Example 1-532.



The title compounds as a yellow solid (5.5 mg, 2 steps 46%) was prepared from the crude compound from step 1-480a (0.015 mmol at most) and 2-(methoxycarbonylamino)-2-phenylbutanoic acid (2.6 mg, 0.015 mmol) using the procedures similar to that described in example 1-528. ESIMS *m/z* = 799.46 $[M+H]^+$.

Example 1-533.

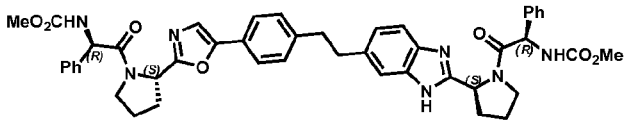


Step 1-533a. A mixture of (S)-tert-butyl 2-(5-(4-bromophenyl)oxazol-2-yl)pyrrolidine-1-carboxylate (prepared according to US2008/311075A1, 47.5 mg, 0.12 mmol) and the compound from step 1-515d (38 mg, 0.12 mg) in triethylamine (10 mL) was added tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol) and copper(I) iodide (2 mg, 0.01 mmol). The resulting mixture was purged with nitrogen before being stirred at 100 °C for 12 hours. The mixture was partitioned between water and EtOAc and the organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown slurry, which was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as a light yellow solid (56 mg, 59%). ESIMS *m/z* = 623.95 $[M+H]^+$.

Step 1-533b. The desired product was prepared from the compound of step 1-533a using procedures similar to that described in step 1-2-1a. ESIMS *m/z* = 424.02 $[M+H]^+$.

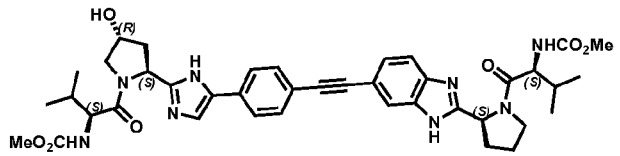
Step 1-533c. The title compound was prepared from the compound of step 1-533b using procedures similar to that described in step 1-2-1b. ESIMS *m/z* = 805.92 $[M+H]^+$.

Example 1-534.



The title compound was prepared from the compound of example 1-533 using procedures similar to that described in example 1-2-2. ESIMS *m/z* = 810.10 $[M+H]^+$.

Example 1-535.



Step 1-535a. The desired product was prepared from (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid using procedures similar to that described in step 1-515a. ESIMS *m/z* = 476.14 $[M+H]^+$.

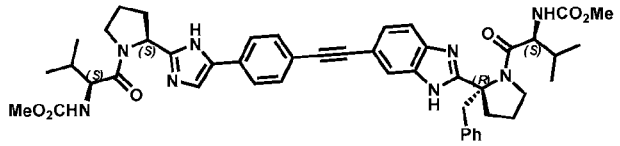
Step 1-535b. The desired product was prepared from the compound of step 1-535a using procedures similar to that described in step 1-515b. ESIMS *m/z* = 455.99 $[M+H]^+$.

Step 1-535c. The desired product was prepared from the compound of step 1-535b and the compound of step 1-515d using procedures similar to that described in step 1-515e. ESIMS *m/z* = 639.30 $[M+H]^+$.

Step 1-535d. The desired product was prepared from the compound of step 1-535c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 439.26 $[M+H]^+$.

Step 1-535e. The title compound was prepared from the compound of step 1-535d and the compound of step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 753.40 $[M+H]^+$.

Example 1-536.



Step 1-536a. The mixture of (R)-2-benzyl-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (200 mg, 0.66 mmol) and 4-bromo-1,2-diaminobenzene (135 mg, 0.73 mmol) in acetonitrile (2 mL) was added EDC (138 mg, 0.73 mmol) and 4-dimethylaminopyridine (40 mg, 0.2 mmol). The resulting mixture was stirred at room temperature for 1 hour before being partitioned between water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to afford a brown slurry, which was purified by flash column chromatography (silica, hexane-EtOAc) to give the desired product as a light yellow solid (190 mg, 61%). ESIMS *m/z* = 474.18 $[M+H]^+$.

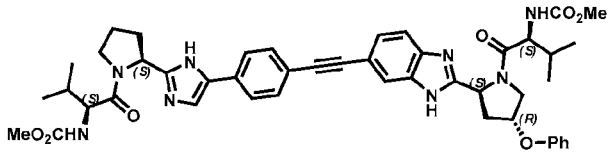
Step 1-536b. The desired product was prepared from the compound of step 1-536a using procedures similar to that described in step 1-1b. ESIMS *m/z* = 456.17 $[M+H]^+$.

Step 1-536c. The desired product was prepared from the compound of step 1-536b and the compound from step **1**-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 713.46 $[M+H]^+$.

Step 1-536d. The desired product was prepared from the compound of step 1-536c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 513.30 $[M+H]^+$.

Step 1-536e. The title compound was prepared from the compound of step 1-536d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 827.49 $[M+H]^+$.

Example 1-537.



Step 1-537a. The desired product was prepared from (2S,4R)-1-(tert-butoxycarbonyl)-4-phenoxypyrrolidine-2-carboxylic acid using procedures similar to that described in step 1-536a. ESIMS *m/z* = 476.14 $[M+H]^+$.

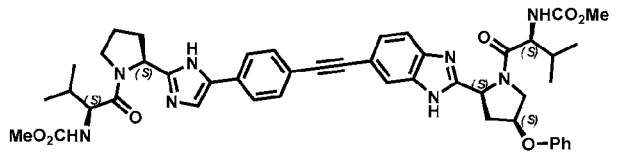
Step 1-537b. The desired product was prepared from the compound of step 1-537a using procedures similar to that described in step 1-1b. ESIMS *m/z* = 458.16 $[M+H]^+$.

Step 1-537c. The desired product was prepared from the compound of step 1-537b and the compound of step 1-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 715.36 $[M+H]^+$.

Step 1-537d. The desired product was prepared from the compound of step 1-537c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 515.19 $[M+H]^+$.

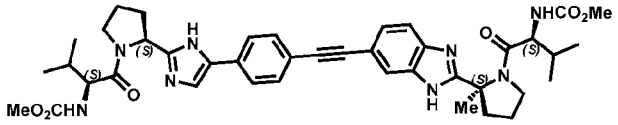
Step 1-537e. The title compound was prepared from the compound from step 1-537d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 829.35 $[M+H]^+$.

Example 1-538.



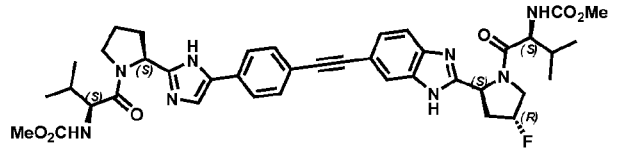
The title compound was prepared from (2S,4S)-1-(tert-butoxycarbonyl)-4-phenoxypyrroli-dine-2-carboxylic acid using procedures similar procedures similar to that described in example 1-537. ESIMS *m/z* = 829.42 $[M+H]^+$.

Example 1-539.



The title compound was prepared from (S)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid using procedures similar procedures similar to that described in example 1-536. ESIMS *m/z* = 751.34 $[M+H]^+$.

Example 1-540.



Step 1-540a. The desired product was prepared from (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid using procedures similar to that described in step 1-536a. ESIMS *m/z* = 402.07 $[M+H]^+$.

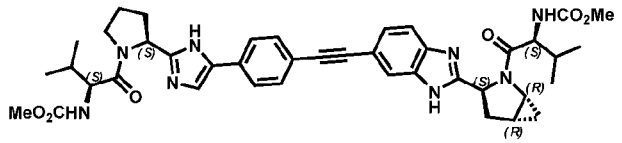
Step 1-540b. The desired product was prepared from the compound from step 1-540a using procedures similar to that described in step 1-1b. ESIMS *m/z* = 384.09 $[M+H]^+$.

Step 1-540c. The desired product was prepared from the compound from step 1-540b and the compound from step 1-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 641.32 $[M+H]^+$.

Step 1-540d. The desired product was prepared from the compound from step 1-540c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 441.13 $[M+H]^+$.

Step 1-540e. The title compound was prepared from the compound from step 1-540d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 755.31 $[M+H]^+$.

Example 1-541.



Step 1-541a. The desired product was prepared from (1R,3S,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (prepared according to WO2009/102325) using procedures similar to that described in step 1-536a. ESIMS *m/z* = 396.13 $[M+H]^+$.

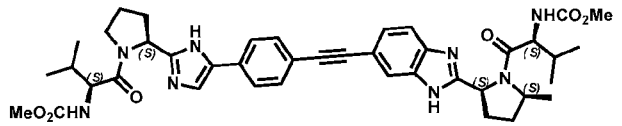
Step 1-541b. The desired product was prepared from compound 1-541a using procedures similar to that described in step 1b. ESIMS *m/z* = 378.11 $[M+H]^+$.

Step 1-541c. The desired product was prepared from the compound from step 1-541b and the compound from step 1-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 635.43 $[M+H]^+$.

Step 1-541d. The desired product was prepared from the compound from step 1-541c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 435.31 $[M+H]^+$.

Step 1-541e. The title compound was prepared from the compound from step 1-541d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 749.45 $[M+H]^+$.

Example 1-542.



Step 1-542a. The desired product was prepared from (2S,5S)-1-(tert-butoxycarbonyl)-5-methylpyrrolidine-2-carboxylic acid (prepared according to *Journal of Medicinal Chemistry* 2009, *49*, 3250) using procedures similar to that described in step 1-536a.. ESIMS *m/z* = 398.07 $[M+H]^+$.

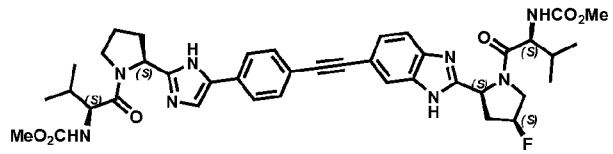
Step 1-542b. The desired product was prepared from the compound from step 1-542a using procedures similar to that described in step 1-1b. ESIMS *m/z* = 380.01 $[M+H]^+$.

Step 1-542c. The desired product was prepared from the compound from step 1-542b and the compound from step 1-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 637.39 $[M+H]^+$.

Step 1-542d. The desired product was prepared from the compound from step 1-542c using procedures similar to that described in step 1-515f. ESIMS *m/z* = 437.26 $[M+H]^+$.

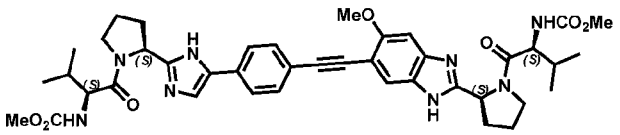
Step 1-542e. The title compound was prepared from the compound from step 1-542d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 751.44 $[M+H]^+$.

Example 1-543.



The title compound was prepared from (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid using procedures similar procedures similar to that described in example 1-540. ESIMS *m/z* = 755.42 $[M+H]^+$.

Example 1-544.



Step 1-544a. The desired product was prepared from (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid and 4-bromo-5-methoxybenzene-1,2-diamine (prepared according to *Journal of Medicinal Chemistry* **1997**, *40*, 730) using procedures similar procedures similar to that described in step 1-536a. ESIMS *m/z* = 414.10 $[M+H]^+$.

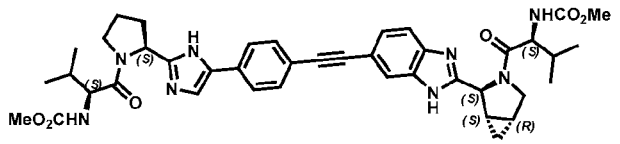
Step 1-544b. The desired product was prepared from the compound from step 1-544a using procedures similar procedures similar to that described in step 1-1b. ESIMS *m/z* = 396.06 $[M+H]^+$.

Step 1-544c. The desired product was prepared from the compound from step 1-544b and the compound from step 1-1-1b using procedures similar procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 653.39 $[M+H]^+$.

Step 1-544d. The desired product was prepared from the compound from step 1-544c using procedures similar procedures similar to that described in step 1-515f. ESIMS *m/z* = 453.27 $[M+H]^+$.

Step 1-544e. The title compound was prepared from the compound from step 1-544d and the compound from step 1-515g using procedures similar procedures similar to that described in step 1-515h. ESIMS *m/z* = 767.47 $[M+H]^+$.

Example 1-545.



Step 1-545a. The desired product was prepared from (1S,2S,5R)-3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (prepared according to *J. Org. Chem*, 1999, *64*, 547) using procedures similar to that described in step 1-536a. ESIMS *m/z* = 396.25 $[M+H]^+$.

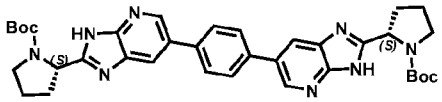
Step 1-545b. The desired product was prepared from the compound from step 1-545a using procedures similar to that described in step 1-1b. ESIMS *m/z* = 378.21 $[M+H]^+$.

Step 1-545c. The desired product was prepared from the compound from step 1-545b and the compound from step 1-1-1b using procedures similar to that described in step 1-1-1c. ESIMS *m/z* = 635.33 $[M+H]^+$.

Step 1-545d. The desired product was prepared from the compound from step 1-545c using procedures similar to that described in step 1f. ESIMS *m/z* = 435.28 $[M+H]^+$.

Step 1-545e. The title compound was prepared from the compound from step 1-545d and the compound from step 1-515g using procedures similar to that described in step 1-515h. ESIMS *m/z* = 749.44 $[M+H]^+$.

Example 2-1.



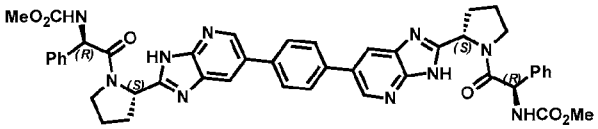
Step 2-1a. A mixture of *N*-Boc-L-proline (2.289 g, 10.6 mmol) and 5-bromo-2,3-diamino-benzene (2.00 g, 10.6 mmol) in DMF (40 mL) were treated with EDC·HCl (2.651 g, 13.8 mmol) and DMAP (0.130 g, 1.06 mmol) at rt for 12 hours and then at 60 °C for another 12 hours. The resultant dark mixture was partitioned (EtOAc - water). The combined organics were washed with brine, dried over Na_2SO_4, filtered and evaporated to give the crude desired compound as a dark brown foam which was directed used in the next step. ESIMS *m/z* = 385.23, 387.23 $[M+H]^+$.

Step 2-1b. A solution of the crude compound from step 2-1a (theo. 10.6 mmol) in glacial acetic acid (100 mL) was heated at 50 °C for 24 hours. The volatiles were evaporated and the resultant dark mixture was partitioned between EtOAc and

saturated aqueous $NaHCO_3$. The organics were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a brown foam (200 mg). ESIMS *m/z* = 267.07, 269.07 $[M+H-Boc]^+$.

Step 2-1c. A mixture of the compound from step 2-1b (78 mg, 0.21mmol), 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (33 mg, 0.10 mmol), $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol), and $NaHCO_3$ (50.4 mg, 0.60 mmol) in 1,2-dimethoxyethane (1 mL) and water (0.5 mL) was heated at 90 °C for 6 hours under N_2 before partition (EtOAc - water). The organics were washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated. The residue was chromatographed (silica, hexane-EtOAc) to give the title compound (8 mg). ESIMS *m/z* = 651.30 $[M+H]^+$.

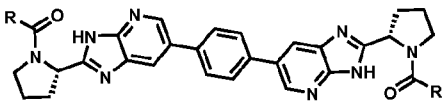
Example 2-2.

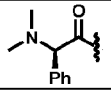


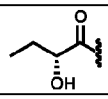
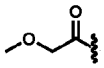
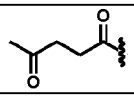
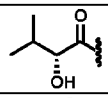
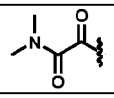
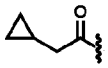
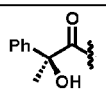
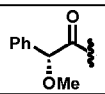
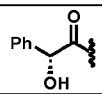
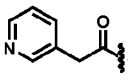
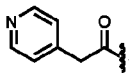
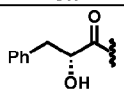
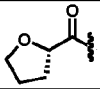
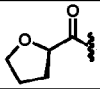
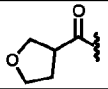
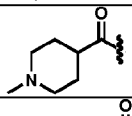
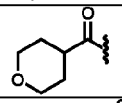
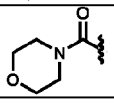
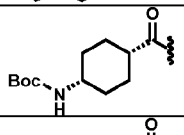
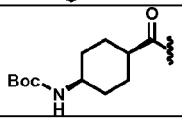
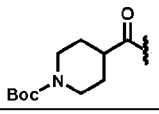
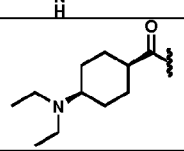
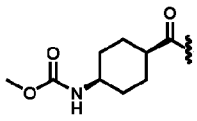
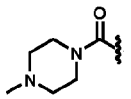
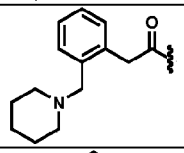
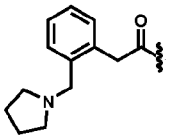
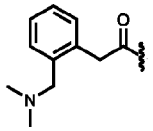
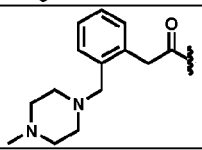
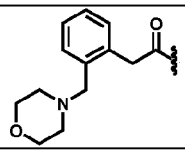
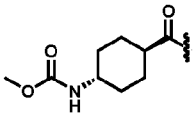
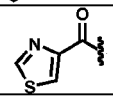
A solution of the compound from example 2-1 (8 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) was treated with hydrogen chloride (4M in dioxane, 5 mL) at rt for 40 minutes before all volatiles were removed by rotavap. The residue was redissolved in DMF (2 mL) and was added DIPEA (0.3 mL, 2.1 mmol), HATU (20 mg, 0.053 mmol) and (*R*)-(methoxycarbonyl)-aminophenyl acetic acid (prepared according to WO 2008/021927, 16 mg, 0.053 mmol). The resulting mixture was stirred at rt for 40 minutes before all volatiles was removed by N_2 flow. The residue was chromatographed (silica, CH_2Cl_2-MeOH) to give the title compound (1.2 mg). ESIMS *m/z* = 833.38 $[M+H]^+$.

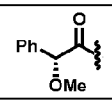
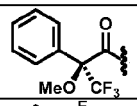
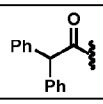
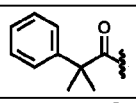
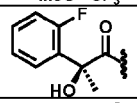
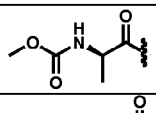
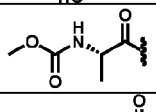
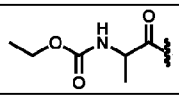
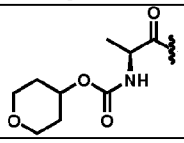
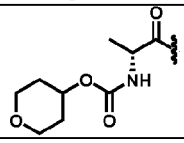
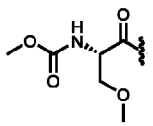
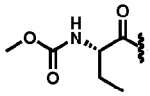
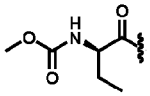
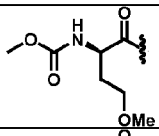
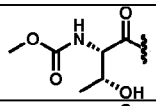
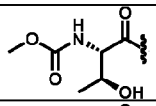
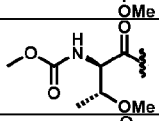
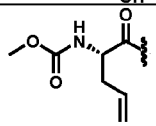
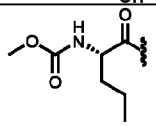
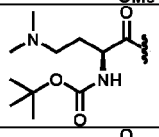
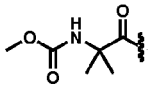
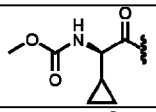
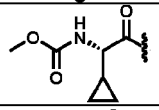
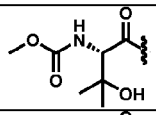
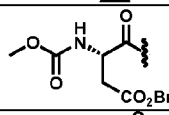
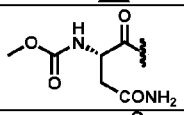
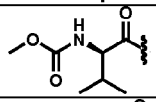
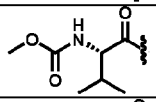
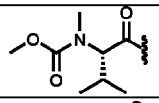
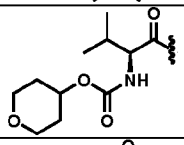
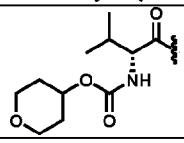
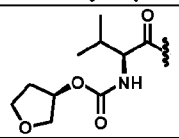
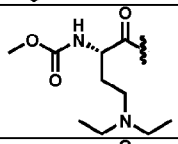
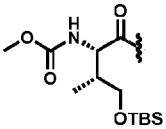
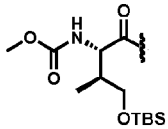
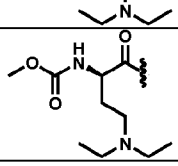
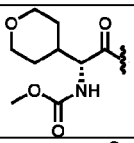
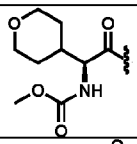
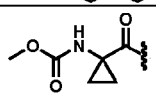
The remaining compounds of examples 2-3 to 2-508 may be prepared using procedures similar to that described in examples 2-1, 2-2, and 2-509 to 2-516, and/or as described in the Synthetic Methods.

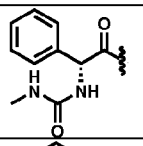
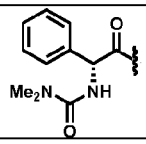
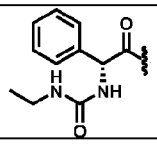
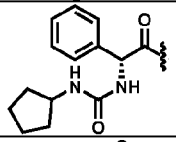
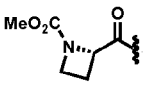
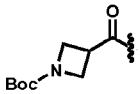
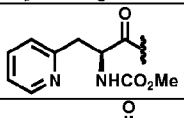
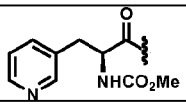
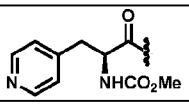
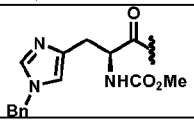
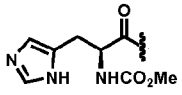
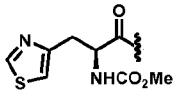
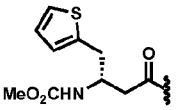
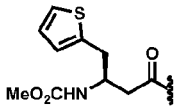
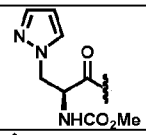
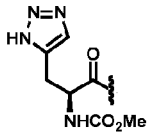
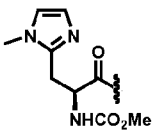
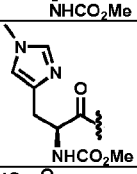
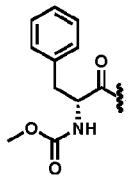
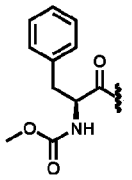
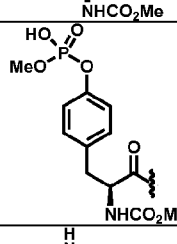
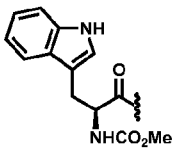
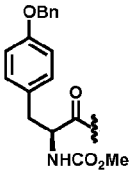
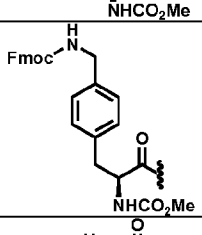
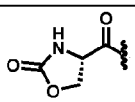
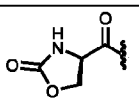
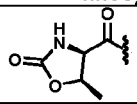
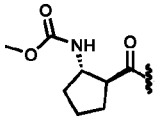
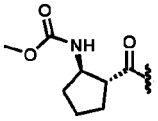
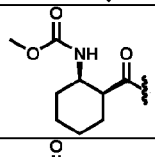
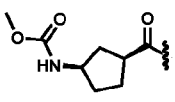
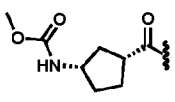
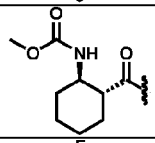
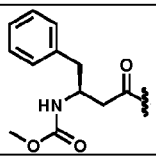
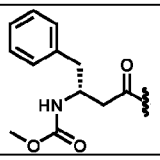
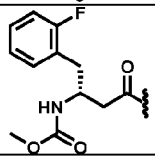
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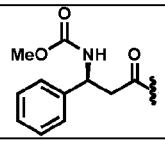
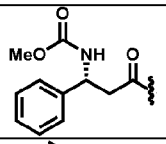
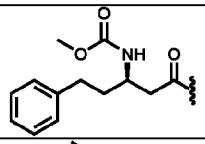
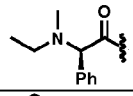
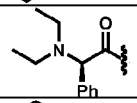
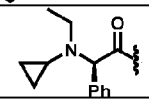
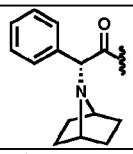
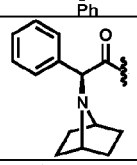
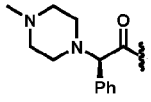
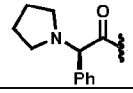
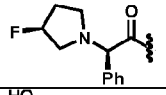
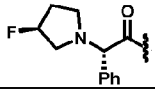
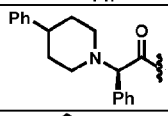
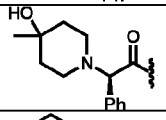
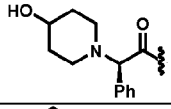
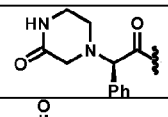
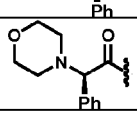
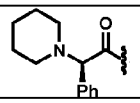
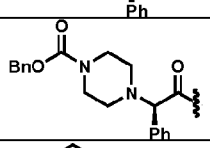
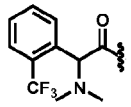
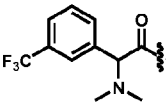
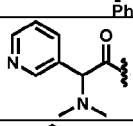
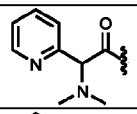
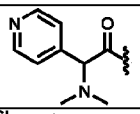
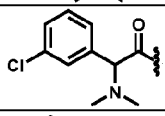
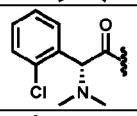
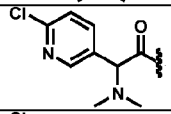
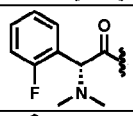
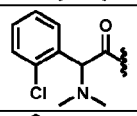
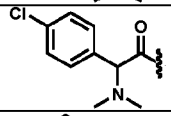
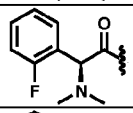
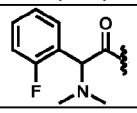
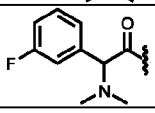
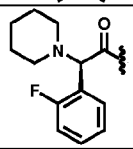
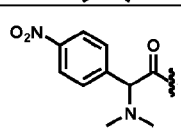
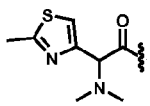
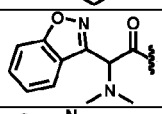
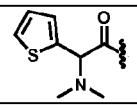
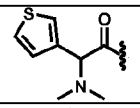
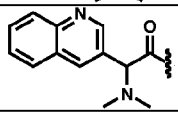


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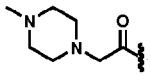
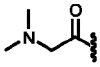
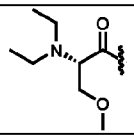
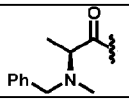
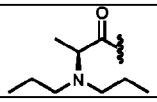
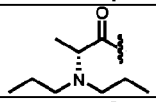
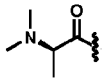
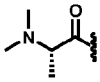
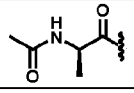
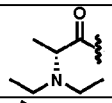
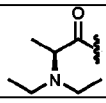
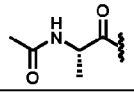
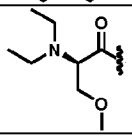
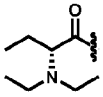
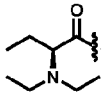
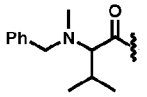
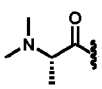
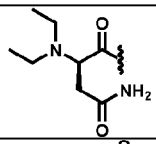
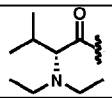
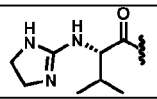
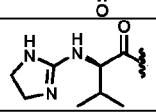
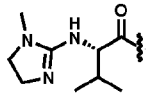
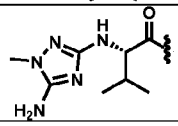
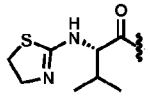
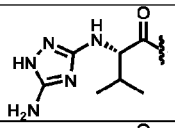
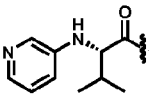
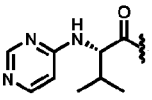
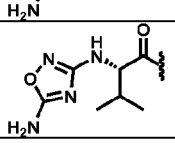
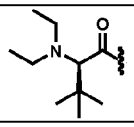
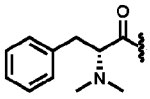
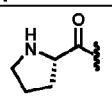
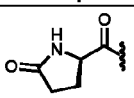
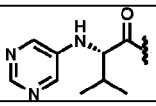
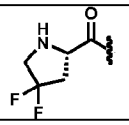
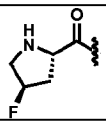
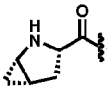
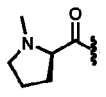
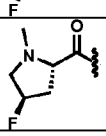
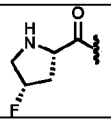
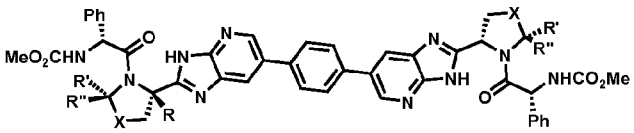
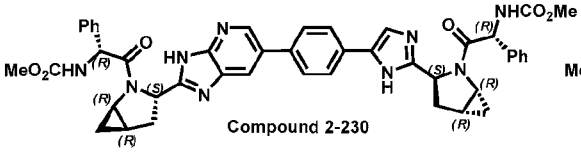
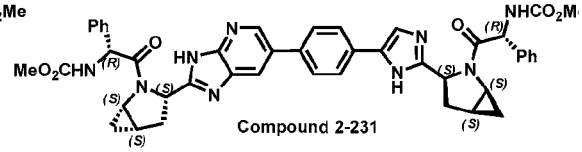
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184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	
202		203		204	
205		206		207	
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211		212		213	
214		215		216	
217		218		219	

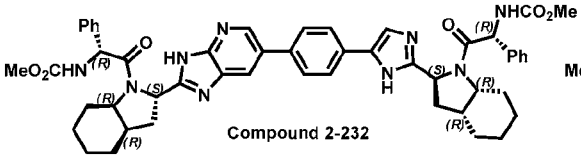
Table 11: Examples 2-220 to 2-229.

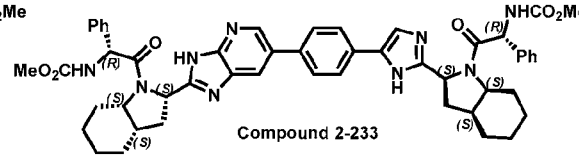


Entry 2-	R	R'	R"	X	Entry 2-	R	R'	R"	X
220	Me	H	H	CH_2	221	H	H	H	CF_2
222	Me	H	H	S	223	H	H	H	
224	Me	H	H	O	225	H	H	H	
226	H	Ph	H	CH_2	227	H	H	H	
228	H	H	Ph	CH_2	229	H	H	H	


Compound 2-230

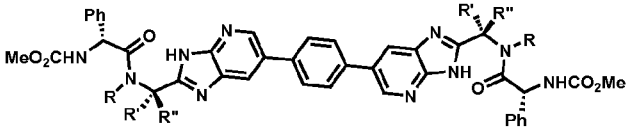

Compound 2-231


Compound 2-232


Compound 2-233

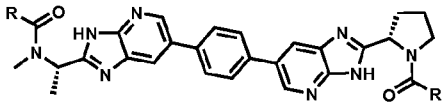
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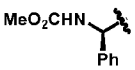
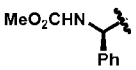
Table 12: Examples 2-234 to 2-243.



Entry 2-	R	R'	R"	Entry 2-	R	R'	R"
234	Me	Me	H	235	H	Me	H
236	Me	H	Me	237	cyclopropyl	Me	H
238	Me	Me	Me	239	Me	cyclopropyl	H
240	Me	Allyl	H	241	Et	Me	H
242	Me	$CHMe_2$	H	243	Me	Et	H

Table 13: Examples 2-244 to 2-263.



Entry 2-	R	R'	Entry 2-	R	R'
244			245		

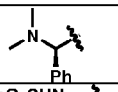
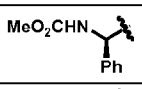
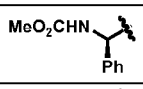
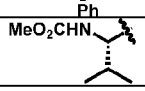
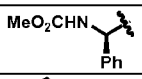
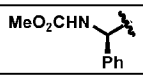
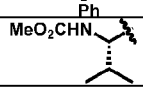
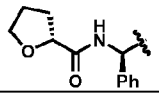
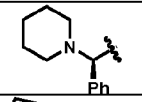
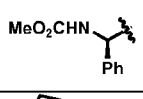
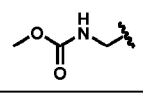
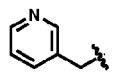
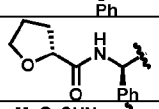
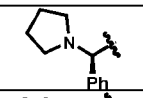
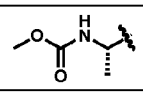
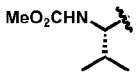
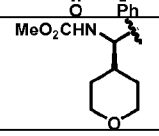
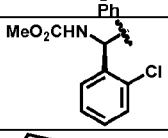
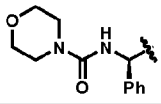
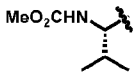
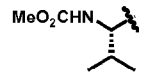
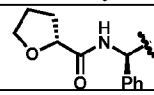
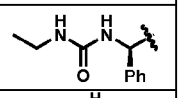
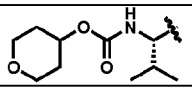
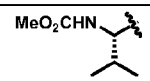
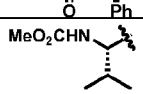
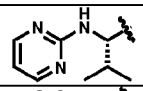
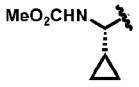
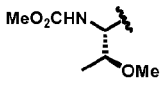
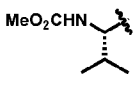
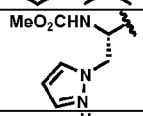
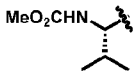
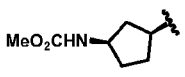
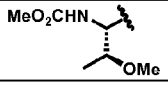
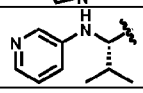
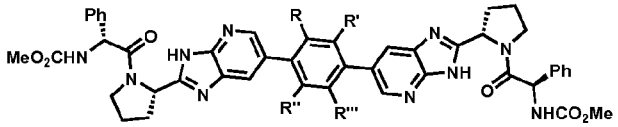
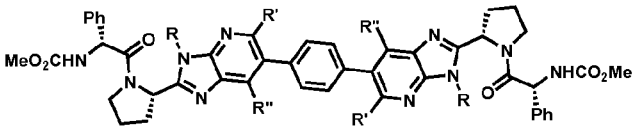
246			247		
248			249		
250			251		
252			253		
254			255		
256			257		
258			259		
260			261		
262			263		

Table 14: Examples 2-264 to 2-273.



Entry 2-	R	R'	R"	R"'	Entry 2-	R	R'	R"	R"'
264	F	H	H	H	265	F	F	H	H
266	Me	H	H	H	267	Me	Me	H	H
268	H	H	Me	Me	269	H	H	Et	Et
270	CF_3	H	H	H	271	CF_3	H	CF_3	H
272	Cl	H	H	H	273	Cl	H	Cl	H

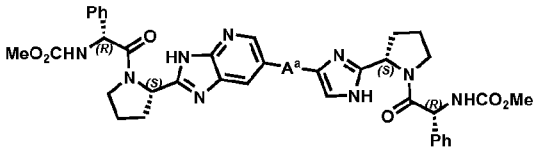
Table 15: Examples 2-274 to 2-291.

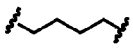
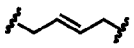
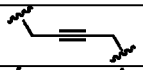
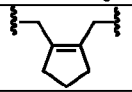
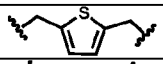
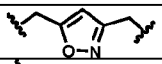
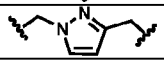
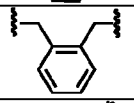
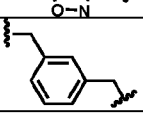
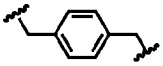
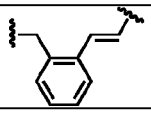
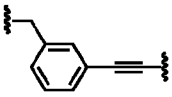
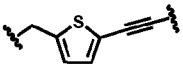
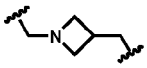
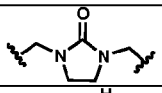
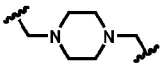
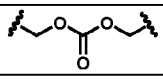
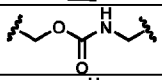
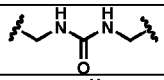
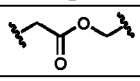
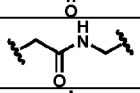
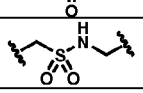
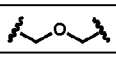
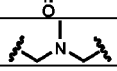
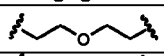
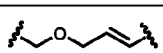
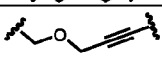
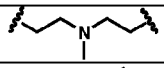
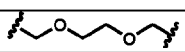
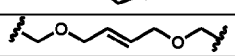
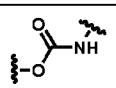
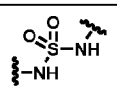
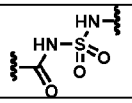
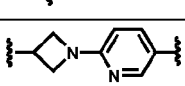
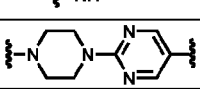
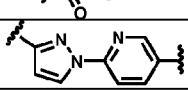


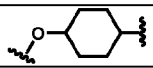
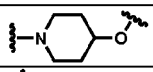
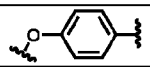
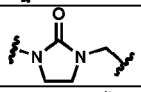
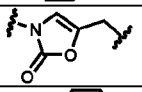
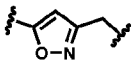
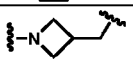
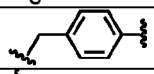
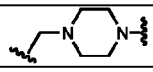
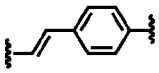
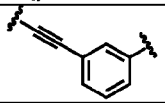
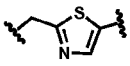
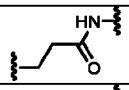
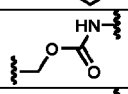
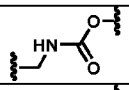
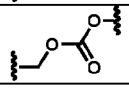
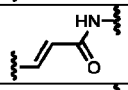
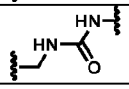
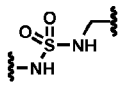
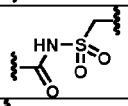
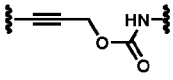
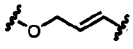
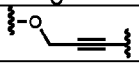
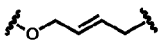
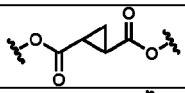
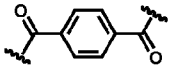
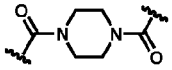
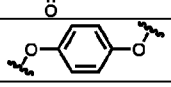
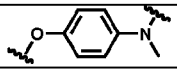
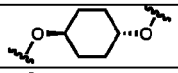
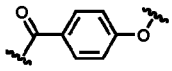
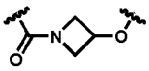
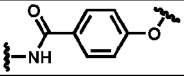
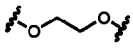
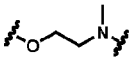
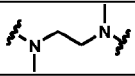
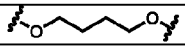
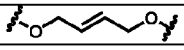
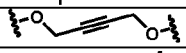
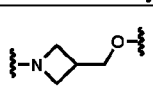
Entry 2-	R	R'	R"	Entry 2-	R	R'	R"
274	Me	H	H	275	H	CO_2H	H
276	H	F	H	277	H	H	CO_2H
278	H	H	F	279	H	CO_2Me	H

280	H	Cl	H	281	H	H	CO_2Me
282	H	H	Cl	283	H	$CONH_2$	H
284	H	Me	H	285	H	H	$CONH_2$
286	H	H	Me	287	H	OMe	H
288	H	CF_3	H	289	H	H	OMe
290	H	H	CF_3	291	CO_2Me	H	H

Table 16: Examples 2-292 to 2-426.



Entry 2-	A^a	Entry 2-	A^a	Entry 2-	A^a
292		293		294	
295		296		297	
298		299		300	
301		302		303	
304		305		306	
307		308		309	
310		311		312	
313		314		315	
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	
337		338		339	

340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	
358		359		360	
361		362		363	
364		365		366	
367		368		369	
370		371		372	
373		374		375	
376		377		378	
379		380		381	
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394		395		396	
397		398		399	

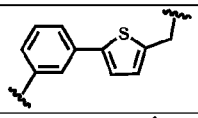
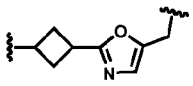
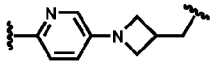
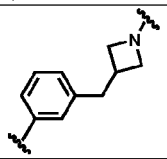
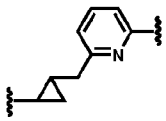
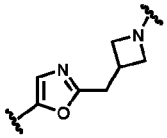
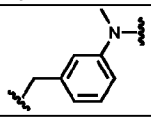
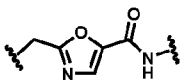
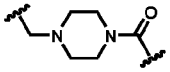
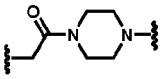
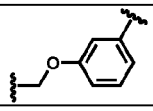
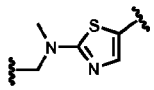
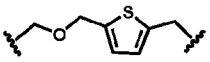
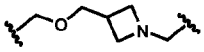
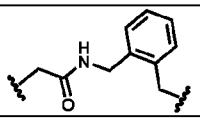
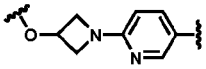
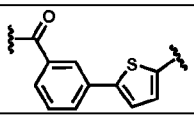
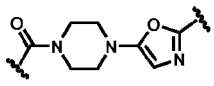
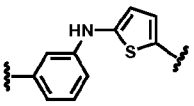
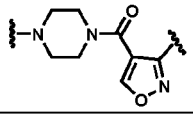
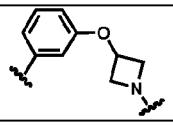
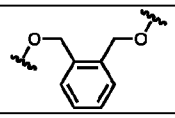
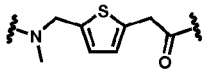
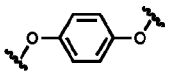
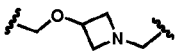
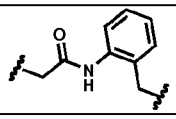
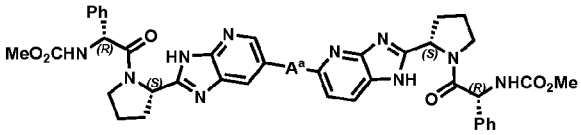
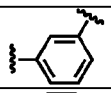
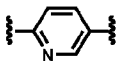
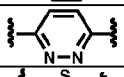
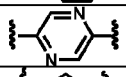
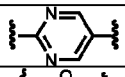
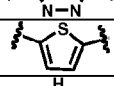
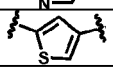
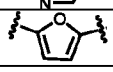
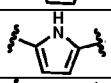
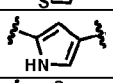
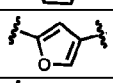
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415		416		417	
418		419		420	
421		422		423	
424		425		426	

Table 17: Examples 2-427 to 2-477.



Entry 2-	A^a	Entry 2-	A^a	Entry 2-	A^a
427		428		429	
430		431		432	
433		434		435	
436		437		438	
439		440		441	
442		443		444	

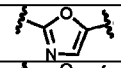
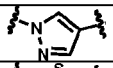
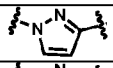
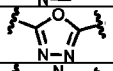
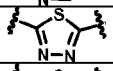
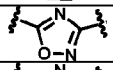
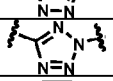
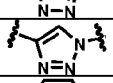
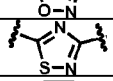
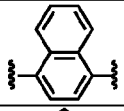
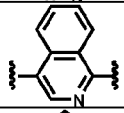
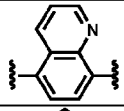
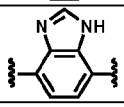
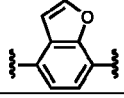
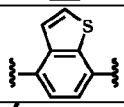
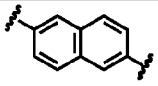
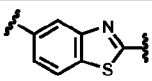
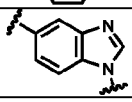
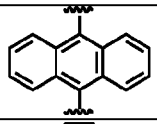
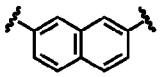
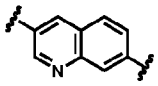
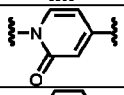
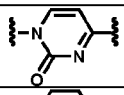
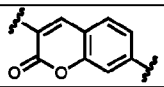
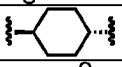
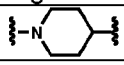
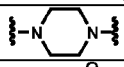
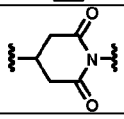
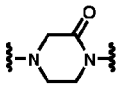
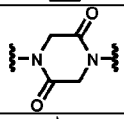
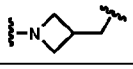
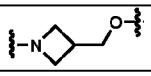
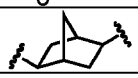
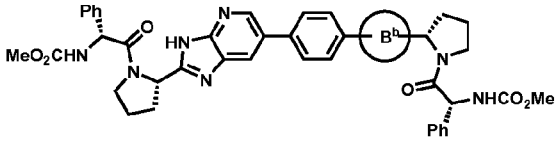
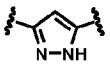
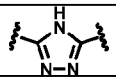
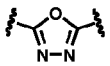
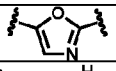
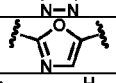
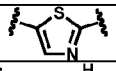
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463		464		465	
466		467		468	
469		470		471	
472		473		474	
475		476		477	

Table 18: Examples 2-478 to 2-497.



Entry 2-	B^b	Entry 2-	B^b	Entry 2-	B^b
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481		482		483	
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487		488		489	
490		491		492	
493		494		495	

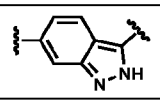
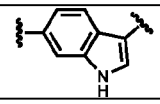
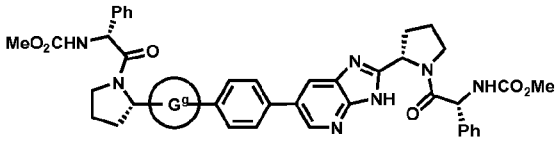
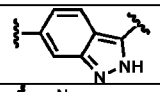
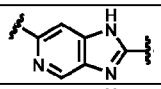
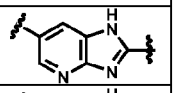
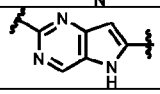
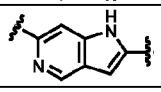
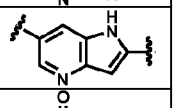
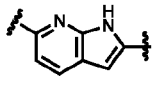
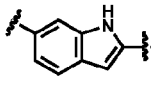
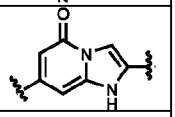
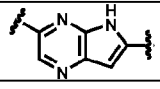
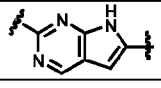
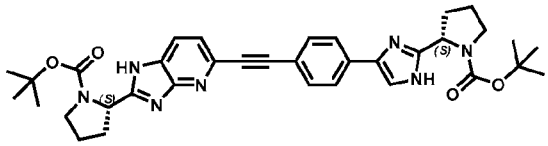
496		497			

Table 19: Examples 2-498 to 2-508.



Entry 2-	G^g	Entry 2-	G^g	Entry 2-	G^g
498		499		500	
501		502		503	
504		505		506	
507		508			

Example 2-509.



Step 2-509a. A mixture of *N*-Boc-L-proline (0.229 g, 1.06 mmol) and TEA (0.15 mL, 1.06 mmol) in THF (10 mL) at −20 °C was treated with *iso*-butyl chloroformate (0.14 mL, 1.06 mmol) for 30 minutes before a slow addition of 6-bromopyridine-2,3-diamine (prepared according to WO 2004/002986 and WO 2008/021851, 0.200 g, 1.06 mmol) in THF (2 mL). It was then kept at −20 °C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a very light brown solid (0.430 g). ESIMS *m/z* = 385.17, 387.17 $[M+H]^+$.

Step 2-509b. A solution of the crude compound from step 2-509a (1.06 mmol at most) in glacial acetic acid (12 mL) was heated at 80 °C for 3 days. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica,

hexanes-ethyl acetate) to give the desired compound as a light yellow solid (0.161 g, 2 steps 41%). ESIMS *m/z* = 367.21, 369.21 $[M+H]^+$.

Step 2-509c. A mixture of 2,4'-dibromoacetophenone (5.00 g, 18.0 mmol), *N*-Boc-L-proline (3.87 g, 18.0 mmol) and in CH_3CN (60 mL) was treated with TEA (5.40 mL, 37.8 mmol) at room temperature until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow foam (6.73 g, 91%). ^1H NMR ($CDCl_3$) 7.76 (t, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 5.0, 8.5 Hz, 2H), 5.51, 5.16 (2d, *J* = 16.0 Hz, 1H), 5.32, 5.28 (2d, *J* = 16.5 Hz, 1H), 4.48, 4.40 (dd, *J* = 5.0, 8.5 Hz, 1H), 3.56 (m, 1H), 3.43 (m, 1H), 2.30 (m, 2H), 2.06 (m, 1H), 1.92 (m, 1H), 1.46, 1.43 (2s, 9H).

Step 2-509d. A solution of the compound from step 2-509c (6.73 g, 16.3 mmol) in toluene (100 mL) was treated with ammonium acetate (25.1 g, 0.327 mol) at 100 °C for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow foam (6.10 g, 95%). ESIMS *m/z* = 392.24, 394.24 $[M+H]^+$. ^1H NMR ($CDCl_3$) 7.57 (bs, 1H), 7.48 (m, 3H), 7.23 (s, 1H), 4.97 (m, 1H), 3.42 (m, 2H), 2.99 (m, 1H), 2.16 (m, 2H), 1.97 (m, 1H), 1.46 (s, 9H).

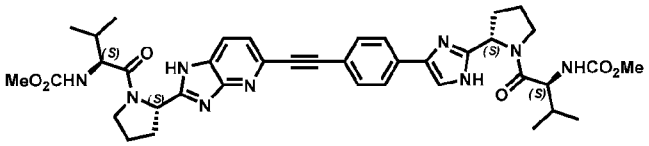
Step 2-509e. A mixture of the compound from step 2-509d (0.559 g, 1.425 mmol), trimethyl-silylacetylene (0.60 ml, 4.275 mmol), CuI (28.5 mg, 0.150 mmol) and $Pd(PPh_3)_2Cl_2$ (80.0 mg, 0.114 mmol) in Et_3N (15 mL) was heated at 80 °C under N_2 for 6 hours before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow foam (0.484 g, 83%). ESIMS *m/z* = 410.24 $[M+H]^+$.

Step 2-509f. A suspension of the compound from step 2-509e (0.484 g, 1.182 mmol) and K_2CO_3 (0.408 g, 2.954 mmol) in methanol (12 ml) was stirred at rt for 3 hour. The volatiles were evaporated off. The residue was purified by chromatography (silica, dichloromethane-ethyl acetate) to give the desired compound as a yellow foam (0.370 g, 93%). ESIMS *m/z* = 338.24 $[M+H]^+$.

Step 2-509g. A mixture of the compound from step 2-509b (23.0 mg, 62.6 μmol), the compound from step 2-509f (23.2 mg, 68.8 μmol), CuI (0.3 mg, 1.8 μmol) and

$Pd(PPh_3)_4$ (3.6 mg, 3.1 μmol) in triethylamine (3 mL) and CH_3CN (3 mL) was degassed and heated to 95 °C under N_2 for 2 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the title compound as a light yellow solid (24.2 mg, 62%). ESIMS *m/z* = 624.48 $[M+H]^+$.

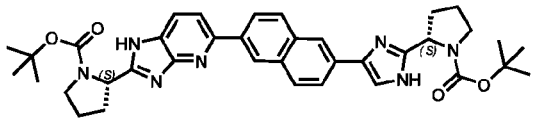
Example 2-510.



Step 2-510a. A solution of the compound of Example 2-509 (38.0 mg, 60.9 μmol) in 1,4-dioxane (1 mL) was treated with HCl in 1,4-dioxane (4 M, 4 mL) rt for 30 min. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was directly used in the next step. ESIMS *m/z* = 424.33 $[M+H]^+$.

Step 2-510b. A mixture of the crude compound from step 2-510a (60.9 μmol at most) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (prepared according to WO 2008/021927, 22.4 mg, 0.129 mmol) in DMF (3 mL) was treated with HATU (46.3 mg, 0.122 mmol) in the presence of DIPEA (0.15 mL, 1.22 mmol) for 2 hours at rt and the volatiles were evaporated off to provide a brown sirup. It was purified by flash column chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a light yellow solid (30.4 mg, 2 steps 68%). ESIMS *m/z* = 738.54 $[M+H]^+$.

Example 2-511.



Step 2-511a. 6-bromo-N-methoxy-N-methyl-2-naphthamide (prepared according to *J. Med. Chem.*, 2006, *49*, 4721-4736, 3.57 g, 12.1 mmol) in THF (60 mL) was treated with methyl magnesium bromide (3M in Et_2O, 8.09 mL, 24.3 mmol) slowly at 0 °C for 1 hour. The solution was warmed up to rt for 2 hours before being quenched with aqueous NH_4Cl. The volatiles were removed and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a white solid (2.89 g, 96%).

Step 2-511b. The compound from step 2-511a (2.89 g, 11.6 mmol) in acetic acid (60 mL) was treated with bromine (0.59 mL, 11.6 mmol) dropwise for 1 hour. The volatiles were evaporated and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a light yellow solid (3.898 g).

Step 2-511c. A mixture of the compound from step 2-511b (at most 11.6 mmol) and *N*-Boc-L-proline (3.75 g, 17.4 mmol) in CH_3CN (60 mL) was added DIPEA (2.89 mL, 23.2 mmol) slowly. The mixture was stirred at rt until the disappearence of the starting material. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a yellow-white foam (4.762 g). ESIMS *m/z* = 462.03, 464.02 $[M+H]^+$.

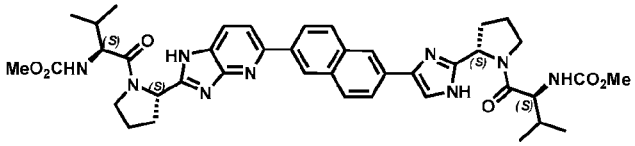
Step 2-511d. A solution of the compound from step 2-511c (at most 11.6 mmol) in toluene (60 mL) was added ammonium acetate (13.4 g, 0.174 mol) and the resultant mixture was heated up at 100 °C for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - aq. $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow brown powder (3.14 g, 4 steps, 61%). ESIMS *m/z* = 442.02, 444.02 $[M+H]^+$.

Step 2-511e. A mixture of the compound from step 2-511d (0.200 g, 0.452 mmol), bis(pinacolato)diboron (0.144 g, 0.565 mmol), $PdCl_2(dppf)_2$ (36.9 mg, 0.0452 mmol) and potassium acetate (88.7 mg, 0.904 mmol) in DMSO (5 mL) was degassed and heated at 80 °C under N_2 for 17 hours. The reaction mixture was allowed to cool down and partitioned (EtOAc - water). The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a yellow solid (0.188 g, 85%). ESIMS *m/z* = 490.12 $[M+H]^+$.

Step 2-511f. A mixture of the compound from step 2-509b (30.0 mg, 81.7 μmol), the compound from step 2-511e (43.9 mg, 89.8 μmol), $Pd(PPh_3)_4$, (4.6 mg, 4.0 μmol) and $NaHCO_3$ (27.5 mg, 0.327 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 95 °C under N_2 for 14 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by

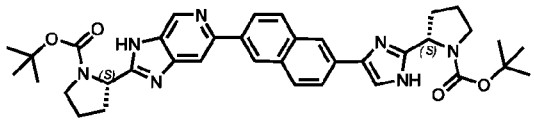
chromatography (silica, hexanes-ethyl acetate) to give the title compound as a white solid (36.6 mg, 69%). ESIMS *m/z* = 650.45 $[M+H]^+$.

Example 2-512.



The title compound was synthesized from the compound from Example 2-511 using procedures similar to that described in Example 2-510. ESIMS *m/z* = 764.67 $[M+H]^+$.

Example 2-513.



Step 2-513a. A mixture of *N*-Boc-L-proline (0.450 g, 2.09 mmol) and TEA (0.29 mL, 2.09 mmol) in THF (20 mL) at −20 °C was treated with *iso*-butyl chloroformate (0.27 mL, 2.09 mmol) for 30 minutes before a slow addition of 6-chloro-3,4-pyridinediamine (0.300 g, 2.09 mmol) in THF (6 mL). It was then kept at −20 °C for 1 hour and then slowly warmed up to rt and stirred at rt overnight. The volatiles were evaporated and the residue was partitioned (EtOAc - water). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a yellow brown foam (0.658 g, 93%). ESIMS *m/z* = 341.21, 343.21 $[M+H]^+$.

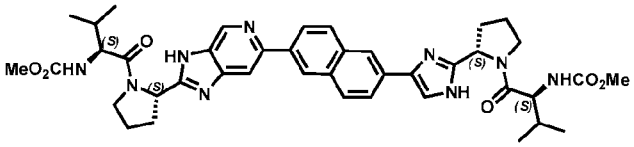
Step 2-513b. A solution of the crude compound from step 2-513a (0.658 g, 1.93 mmol) in glacial acetic acid (12 mL) was heated at 120 °C for 24 hours. The volatiles were evaporated off and the residue was partitioned (EtOAc - saturated aqueous $NaHCO_3$). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude desired compound as a light yellow oil which was directly used in the next step. ESIMS *m/z* = 265.16 $[M+H]^+$.

Step 2-513c. The crude compound from step 2-513b (1.93 mmol at most) in aqueous 2N HCl (20 mL) was heated at 100 °C for 2 hours before being evaporated to dryness. The residue was co-evaporated with methanol twice and then CH_2Cl_2 twice to give the crude desired compound as a light yellow oil which was directly used in the next step. ESIMS *m/z* = 223.12 $[M+H]^+$.

Step 2-513d. The crude compound from step 2-513c (1.93 mmol at most) in CH_2Cl_2 (16 mL) was treated with triethyl amine (2.70 mL, 19.3 mmol), di-tert-butyl dicarbonate (1.09 g, 5.02 mmol) and DMAP (23.6 mg, 0.193 mmol) for 14 hours before being evaporated to dryness. The residue was purified by flash column chromatography (silica, hexanes-ethyl acetate) to give the desired compound as a light yellow oil (0.510 g, 3 steps 63%). ESIMS *m/z* = 423.24 $[M+H]^+$.

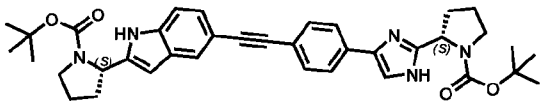
Step 2-513e. A mixture of the compound from step 2-513d (94.0 mg, 0.222 mmol), the compound from step 2-511e (0.119 g, 0.245 mmol), $Pd(PPh_3)_4$, (25.7 mg, 22.2 μmol) and $NaHCO_3$ (74.7 mg, 0.889 mmol) in DME (6 mL) and H_2O (2 mL) was degassed and heated at 95 °C under N_2 for 20 hours. The volatiles were evaporated and the residue was partitioned (EtOAc - H_2O). The organics were washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate) to give the title compound as a brown solid (52.1 mg, 36%). ESIMS *m/z* = 650.40 $[M+H]^+$.

Example 2-514.



The title compound was synthesized from the compound from Example 2-513 using procedures similar to that described in Example 2-510. ESIMS *m/z* = 764.57 $[M+H]^+$.

Example 2-515.



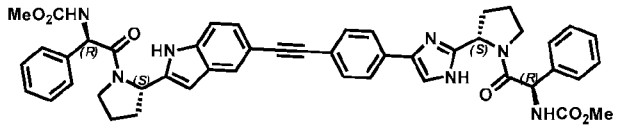
Step 2-515a. A mixture of 4-bromo-2-iodoaniline (0.839 g, 2.817 mmol), *tert*-butyl (2*S*)-2-ethynylpyrrolidine-1-carboxylate (0.500 g, 2.561 mmol), CuI (14.6 mg, 0.0768 mmol) and $Pd(PPh_3)_2Cl_2$ (90.0 mg, 0.128 mmol) in Et_3N (15 mL) was degassed and stirred at rt under N_2 for 3.5 hours before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a light brown foam (0.741 g, 79%). ESIMS *m/z* = 365.09, 367.09 $[M+H]^+$.

Step 2-515b. A mixture of the compound from step 2-515a (0.621 g, 1.700 mmol) and $Cu(OAc)_2$ (61.8 mg, 0.340 mmol) in 1,2-dichloroethane (10 ml) was heated at

150 °C with a microwave for 30 minutes. The mixtrue was combined with another batch (0.120 g of the compound from step 1a) and directly purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the desired compound as a yellow foam (0.625 g, 84%). ESIMS *m/z* = 365.09, 367.09 $[M+H]^+$.

Step 2-515c. A mixture of the compound from step 2-515b (60.0 mg, 0.164 mmol), the compound from step 2-509f (61.0 mg, 0.181 mmol), CuI (1.6 mg, 8.21 μmol) and $Pd(PPh_3)_2Cl_2$ (11.5 mg, 0.0164 mmol) in Et_3N (3 mL) was degassed and heated at 85 °C under N_2 overnight before being evaporated. The residue was purified by chromatography (silica, hexanes-ethyl acetate with 1% Et_3N in ethyl acetate) to give the title compound as a yellow solid (5.5 mg, 5.4%). ESIMS *m/z* = 622.17 $[M+H]^+$.

Example 2-516.



Step 2-516a. A solution of the compound of example 2-515 (5.5 mg, 8.46 μmol) in 1,4-dioxane (0.5 mL) was treated with HCl in 1,4-dioxane (4 M, 2 mL) at rt for 1 hour. The volatiles were evaporated off to give the crude desired compound as a yellow solid which was used directly in the next step.

Step 2-516b. A mixture of the crude compound from step 2-516a (8.46 μmol at most) and (*R*)-(methoxycarbonyl)amino phenyl acetic acid (prepared according to WO 2008/021927, 4.6 mg, 0.0221 mmol) in DMF (0.5 mL) was treated with HATU (7.7 mg, 0.0204 mmol) in the presence of DIPEA (0.03 mL, 0.177 mmol) for 2 hours at rt and the volatiles were evaporated off. It was purified by chromatography (silica, CH_2Cl_2-MeOH) to give the title compound as a yellow solid (2.6 mg, 2 steps 37%). ESIMS *m/z* = 804.10 $[M+H]^+$.

BIOLOGICAL ACTIVITY

1. HCV Replicon Cell Lines

HCV replicon cell lines (kindly provided by R. Bartenschlager) isolated from colonies as described by Lohman et. al. (Lohman et al. (1999) Science 285: 110-113, expressly incorporated by reference in its entirety) and used for all experiments. The HCV replicon has the nucleic acid sequence set forth in EMBL Accession No.: AJ242651, the coding sequence of which is from nucleotides 1801 to 8406.

The coding sequence of the published HCV replicon was synthesized and subsequently assembled in a modified plasmid pBR322 (Promega, Madison, WI) using standard molecular biology techniques. One replicon cell line ("SGR 11-7") stably expresses HCV replicon RNA which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the neomycin phosphotransferase gene (neo), (iii) the IRES from encephalomyocarditis virus (EMCV), and (iv) HCV NS2 to NS5B genes and the HCV 3'UTR. Another replicon cell line ("Huh-luc/neo-ET") described by Vrolijk et. al. (Vrolijk et. al. (2003) Journal of Virological Methods 110:201-209, expressly incorporated by reference in its entirety) stably expresses HCV replicon RNA which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the firefly luciferase reporter gene, (iii) the ubiquitin gene, (iv) the neomycin phosphotransferase gene (neo), (v) the IRES from encephalomyocarditis virus (EMCV), and (vi) HCV NS3 to NS5B genes that harbor cell culture adaptive mutations (E1202G, T1280I, K1846T) and the HCV 3'UTR.

These cell lines were maintained at 37°C, 5% CO_2, 100% relative humidity in DMEM (Cat# 11965-084, Invitrogen), with 10% fetal calf serum ("FCS", Invitrogen), 1% non-essential amino acids (Invitrogen), 1% of Glutamax (Invitrogen), 1% of 100X penicillin/streptomycin (Cat# 15140-122, Invitrogen) and Geneticin (Cat# 10131-027, Invitrogen) at 0.75 mg/ml or 0.5 mg/ml for 11-7 and Huh-luc/neo-ET cells, respectively.

2. HCV Replicon Assay - qRT-PCR

EC_{50} values of single agent compounds and combinations were determined by HCV RNA detection using quantitative RT-PCR, according to the manufacturer's instructions, with a TaqMan® One-Step RT-PCR Master Mix Reagents Kit (Cat# AB 4309169, Applied Biosystems) on an ABI Model 7500 thermocycler. The TaqMan primers used for detecting and quantifying HCV RNA were obtained from Integrated DNA Technologies. HCV RNA was normalized to GAPDH RNA levels in drug-treated cells, which is detected and quantified using the Human GAPDH Endogenous Control Mix (Applied Biosystems, AB 4310884E). Total cellular RNA is purified from 96-well plates using the RNAqueous 96 kit (Ambion, Cat# AM1812). Chemical agent cytotoxicity is evaluated using an MTS assay according to the manufacturer's directions (Promega).

3. HCV Replicon Assay - Luciferase

Since clinical drug resistance often develops in viral infections following single agent therapies, there is a need to assess the additive, antagonistic, or synergistic properties of combination therapies. We used the HCV replicon system to assess the potential use of the compound of the present invention or in combination therapies with Interferon alpha, cyclosporine analogs and inhibitors targeting other HCV proteins. The acute effects of a single or combinations of drugs are studied in the "Huh-luc/neo-ET" replicon with each chemical agent titrated in an X or Y direction in a 6 point two-fold dilution curve centered around the EC50 of each drug. Briefly, replicon cells are seeded at 7,000 cells per well in 90 ul DMEM (without phenol red, Invitrogen Cat.# 31053-036) per well with 10% FCS, 1% non-essential amino acids, 1% of Glutamax and 1% of 100X penicillin/streptomycin and incubated overnight at 37°C, 5% CO_2, 100% relative humidity. 16-20h after seeding cells, test compounds previously solubilized and titrated in dimethyl sulfoxide ("DMSO") from each X plate and Y plate are diluted 1:100 in DMEM (without phenol red, Invitrogen Cat.# 31053-036) with 10% FCS, 1% non-essential amino acids, 1% of Glutamax and 1% of 100X penicillin/streptomycin and added directly to the 96-well plate containing cells and growth medium at a 1:10 dilution for a final dilution of compound and DMSO of 1:1000 (0.2% DMSO final concentration). Drug treated cells are incubated at 37°C, 5% CO_2, 100% relative humidity for 72 hours before performing a luciferase assay using 100 ul per well BriteLite Plus (Perkin Elmer) according to the manufacturer's instructions. Data analysis utilizes the method published by Prichard and Shipman (Antiviral Research, 1990. 14:181-205). Using this method, the combination data are analyzed for antagonistic, additive, or synergistic combination effects across the entire combination surface created by the diluted compounds in combination.

The compounds of the present invention may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present invention inhibit HCV replicon and in another embodiment the compounds of the present invention inhibit NS5A.

The compounds of the present invention can be effective against the HCV 1b genotype. It should also be understood that the compounds of the present invention can inhibit multiple genotypes of HCV. In one embodiment, compounds of the present invention are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. Table 22 shows the EC_{50} values of representative compounds of the present

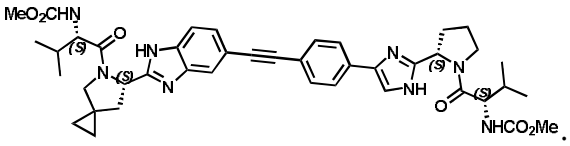
invention against the HCV 1b genotype from the above described qRT-PCR or luciferase assay. EC_{50} ranges against HCV 1b are as follows: A >10 nM; B 1-10 nM; C < 1nM.

Table 22: Genotype-1b replicon EC_{50}

Example	Range	Example	Range	Example	Range
1-2	C	1-2-1	C	1-2-2	C
1-357	C	1-442	C	1-443	C
1-445	C	1-446	C	1-448	C
1-449	C	1-451	C	1-453	C
1-454	C	1-456	C	1-457	C
1-459	C	1-460	C	1-463	C
1-464	C	1-465	C	1-466	C
1-468	C	1-469	C	1-471	C
1-472	C	1-473	C	1-475	C
1-477	C	1-479	C	1-480	C
1-481	C	1-483	C	1-485	C
1-486	C	1-488	C	1-490	C
1-492	C	1-493	C	1-494	C
1-497-a	C	1-497-b	C	1-499	C
1-500	B	1-501	C	1-502	C
1-503	C	1-504	C	1-505	C
1-506	C	1-507	C	1-508	C
1-509	C	1-510	C	1-511	C
1-512	C	1-513	C	1-514	C
1-515	C	1-517	C	1-519	C
1-521	C	1-523	C	1-525	C
1-526	C	1-527	C	1-528	C
1-529	C	1-530	C	1-531	C
1-532	C	1-533	C	1-534	C
1-535	C	1-536	C	1-537	C
1-538	C	1-539	C	1-540	C
1-541	C	1-542	C	2-2	C
2-510	C	2-512	C	2-516	C

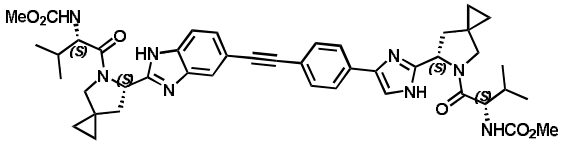
CLAIMS

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. A compound of formula:



or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

4. A pharmaceutical composition comprising a compound according to claim 2, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.